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LETTER FROM THE FORMER MANAGING EDITOR

To our subscribers:

The delay in publication of recent issues of this JOURNAL has been due to a shortage of enamel paper. During the War, the Banta Press fortunately provided us with what was necessary from a generous stock-pile, but difficulty in replenishing it has caused the present delay, which we hope will not be repeated.

Last year at this time a shortage of manuscripts caused delay, but at present, although not overnumerous, there are several manuscripts that each month succeed in impressing our observant Editors.

In this number is presented a very interesting work by Greenwald, who properly and refreshingly reopens a highly important and controversial subject. Anyone who recalls the work presented at the last International Goiter Congress will be highly stimulated. In presenting this, we do not—and certainly he does not—intend to fall into the same pitfall as the French Academy of the Eighteen-Fifties, and consider the matter closed.

KENNETH WADE THOMPSON, M.D.
September 11, 1946

IS ENDEMIC GOITER DUE TO A LACK OF IODINE?

ISIDOR GREENWALD

(From the Department of Chemistry, New York University College of Medicine)

I. INTRODUCTION

THE author (36) has recently presented evidence indicating that goiter did not exist in the Americas or in New Zealand before the coming of white men nor in England before the eighteenth century. Moreover, the temporal variations in the incidence of goiter at various places in North America, and elsewhere, seem inconsistent with the view that lack of iodine in food, or water, or both, is the only, or even the chief, cause of goiter (36).

These findings have prompted a re-examination of the evidence upon which that hypothesis rests. The results have been startling and appear to be of sufficient importance to warrant publication.

The hypothesis that endemic goiter is due to a lack of iodine seems to have been first presented by Prevost (79), apparently without any evidence in its support other than the successful use of iodine and, before the discovery of the element, of burnt sponge, in the treatment of goiter by a number of physicians. Shortly thereafter, Chatin (17) presented the results of a large number of analyses of water, air and foods in a series of reports, mostly between 1850 and 1860. Their publication was followed by a widespread use of iodine in the treatment of goiter. The amounts used seem to have been large. The results were not satisfactory, and the treatment fell into disrepute and was not revived until after Baumann's discovery of iodine in the thyroid (10) provided a new reason for its use. When it was reported that the prophylactic use of smaller amounts of iodine than had previously been used for therapeutic purposes reduced the incidence of goiter in regions in which it was endemic (55), interest in Chatin's hypothesis was naturally revived and led to a very large number of analyses which, in the opinion of those who published them, confirmed the hypothesis.

Before proceeding to a discussion of these mainstays of the "iodine-lack" hypothesis, it seems desirable to examine three corollaries that follow from the proposition that "The immediate cause of the thyroid enlargement is a relative or an absolute deficiency of iodine" (68[1]), or "the immediate

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[1] Page 108.

cause of goiter is failure of the thyroid gland to obtain an adequate supply of iodine" (38[2]). These are:

1. Goitrous individuals should have low metabolic rates.
2. Goiters should contain less iodine than do normal glands, not only per gram of tissue, but per entire gland.
3. It should be possible a) to produce goiter in animals by placing them on iodine-poor diets, and b) to prevent it by the addition to such diets of such small amounts of iodine as are found in ordinary foods.

None of these corollaries, with the possible exception of 3a, is true.

II. THE METABOLIC RATE IN SIMPLE GOITER

In contrast to the well established effect of total thyroidectomy or of spontaneous degeneration (myxedema), the basal metabolic rate in simple goiter is quite normal. Elmer and Scheps (24) in 11 cases found it to vary between +11 and −27 per cent of the normal; the average was −8 per cent. Lunde, Closs and Wülfert (62) reported values of from 105 to 115, average 110 per cent of normal, in eight cases. In 120 cases of simple goiter, Webster (101) found the average basal metabolic rate to be −12 per cent as compared with the Aub-Dubois standards. Boothby and Plummer (14) (p. 874), wrote: "The basal metabolic rate usually is within normal limits or possibly more frequently toward the lower than toward the upper limits of normality."

III. THE IODINE CONTENT OF NORMAL AND OF ENLARGED THYROIDS

There are records of some large goiters in which the iodine concentration was very low and for which the earlier analysts reported only "traces" to be present. However, it is the total content, and not the concentration, that indicates whether or not enough iodine was available. If the total iodine content of goiters is as high as that of normal glands, it is impossible to regard a lack of iodine as being responsible for the development of the goiter. It is, therefore, highly significant that, almost without exception, the *total iodine content* of goiters is fully as great as, or even more than, that of normal glands in the same region.

Moreover, if the "iodine-lack" hypothesis were correct, a small deficiency in iodine, while not grave enough to cause the formation of a huge goiter, should result in an enlargement of the thyroid. In consequence, statistical analysis of the weights of the glands and of their iodine contents should reveal a negative correlation between the two sets of figures.

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[2] Page 69.

TABLE 1. CORRELATION BETWEEN SIZE AND IODINE CONTENT OF THYROID GLANDS

Author and Reference Number	Locality	Number	Weight[1]			Iodine content			Coefficient of Correlation
			Min. gm.	Max. gm.	Av. gm.	Min. mg.	Max. mg.	Av. mg.	
Baumann (10)	Freiburg	26	*3.1*	*12.0*	*2.5*	trace[2]	7.2[3]	2.5	0.06
	Hamburg	30	*1.5*	*19.0*	4.6	trace[2]	9.7	3.8	0.55
	Berlin	11	*3.1*	*11.0*	7.4	1.7	9.9	6.6	0.88
Oswald (78)	Geneva	22	18.0	95.5	53.4	1.7	25.6	9.3	0.37
	Lausanne	10[4]	19.0	91.5	63.5	0.7	22.7	8.0	0.02
	Basel	16[4]	22.0	95.0	46.2	2.3	17.7	5.8	0.70
	Zurich	23[4]	31.0	92.0	59.1	3.2	24.7	10.3	0.32
	Berne	18	27.0	91.5	57.0	1.6	24.8	13.0	0.12
	Geneva[5]	8	111.0	235.0	158.0	2.8	54.1	24.1	
	Lausanne[5]	9	140.0	409.0	271.0	0.5	94.5	26.9	
	Basel[5]	2	106.0	157.0	132.0	10.2	13.5	11.9	
	Zurich[5]	6	109.0	213.0	152.0	6.2	38.0	17.2	
	Berne[5]	7	105.0	554.0	199.0	2.6	56.6	15.9	
Wells (103)	Chicago	20	*2.6*	*10.6*	*5.4*	4.3	17.8	10.4	0.23
	Boston and New York	12	*3.4*	*6.4*	*4.5*	6.9	18.0	11.7	0.20
Weiss (102)	Breslau	50[6]	*1.8*	*15.5*	*7.2*	0.75	11.5	4.04	0.1
v. Rositzky (88)	Styria	17[7]	33.0	231.0	91.0	0.73	17.4	5.65	0.7
Aeschbacher (3)	Chaux de Fonds	57[8]	14.0	77.0	36.5	0.3	24.1	6.65	0.16
Jolin (53)	Upsala	146[9]	*1.59*	*31.55*	*7.08*	0.4	59.8	11.05	0.41
Claude and Blanchetiere (18)	Paris	39	7.3[10]	104.5	23.8	0.4	15.7	3.9	0.29
Morgenstern (74)	Zurich	32[11]	16.2	394.0	83.4	0.75	37.1	8.47	0.39
Zuns (104)	Belgium	55[12]	*2.1*	*40.5*	*7.8*	3.2	47.5	16.5	0.84
Müller (75)	Zurich	111[13]	17.0	331.0	77.0	none[2]	54.0	5.9	0.25
Herglos (44)	Budapest	20	18.3	84.3	36.9	1.08	25.7	8.06	0.4
Jansen and Robert (51)	Munich	26	23.0	553.0	121.0	0.9	14.6	5.9	0.14[14]
Remington, et al. (85)	Charleston, S. Carolina	28[15]	10.0	35.0	17.1	2.49	23.7	8.7	0.14
Straub and Papp (97)	Hungary	41[16]	9.5	55.0	24.6	0.44	14.4	3.94	0.53
Mitsui (73)	Japan	141[17]	4.5	56.6	14.9	1.1	28.8	11.1	0.57
Leland and Foster (57)	New York	52	9.0	47.0	20.7	0.95	25.0	8.10	0.76
Andreassi and Talenti (4)	Rome	30	8.9	30.5	17.6	1.2	9.2	4.6	0.05
Marine and Williams (71)	Cleveland	77[18]	**0.95**	**6.77**	**1.14**	**0.02**	**12.3**	**0.13**	**0.35**

[1] Italic figures give dry weight; those in bold-face (last line) give weight per kilogram of body weight; all others refer to fresh weight.

[2] In the calculations, "traces" have been counted as zero.

[3] Baumann arbitrarily rejected all thyroids containing more than 10 mg. of iodine because he considered that this high content of iodine was presumptive evidence of iodine medication. This interpretation is open to serious doubt in at least two cases in which the dry thyroids weighed 9.3 gm. and 10.7 gm. and contained 35.3 mg. and 14.9 mg. of iodine, respectively, because the individuals had been patients in the University Hospital at Freiburg for 2.5 months and six weeks, respectively, prior to death, with known freedom from iodine medication.

[4] There were 2, 5, and 3 others, respectively, for which the dry weights, but not the fresh weights, are given. Inclusion of these would change the averages for the iodine contents to 7.07 mg., 6.48 mg., and 10.27 mg., respectively.

[5] These data are for goiters, all of which weighed over 100 gm.

[6] In addition, there were 9 goiters, the dry weight of which varied from 20.5 gm. to

In Table 1, there have been collected all the pertinent data, from the time of Baumann, who discovered iodine in the thyroid in 1896, to 1934, the date of the latest publication on the subject. The figures reported by

52 gm. The total iodine content varied from "traces" to 11.0 mg. The average, considering "traces" to be "zero," was 6.0 mg., one and one-half times the average in the normal glands.

[7] There were two thyroids weighing 145 gm. and 54 gm. and containing 27.5 mg. and 54.7 mg. of iodine, respectively, that have been omitted from the table because of their high iodine content, although von Rositzky stated that there was no history of iodine medication. Of the 17 thyroids remaining, 8 were classified by von Rositzky as goiters. These varied in weight from 91 gm. to 231 gm. and contained from 3.38 mg. to 17.4 mg., average 8.4 mg. of iodine. The nine normal glands varied in weight from 29 gm. to 60 gm., average 41 gm., and contained from 0.73 mg. to 6.21 mg., average 3.21 mg. of iodine.

[8] Aeschbacher presents data for 61 thyroids. Three were from children 5, 8, and 8 years old and have been omitted as have also the data for another weighing 88 gm., and containing 51.6 mg. of iodine. The inclusion of the latter would only have raised the value of the correlation coefficient.

[9] All the data from individuals less than 19 years of age have been omitted.

[10] Sclerosed gland, showing little colloid.

[11] Only those from adults have been included. Two, weighing 16 gm. and 42 gm., respectively, in which analyses showed only "traces" of iodine have been omitted. Their inclusion would only have increased the value of the coefficient of correlation. This series contained 11 goiters varying from 30 to 394 gm. in weight and containing from 0.75 mg (1.0 mg. in the largest, partly calcified gland) to 11.3 mg., average 6.78 mg. of iodine. The remaining 21 glands varied in weight from 16.2 gm. to 91 gm., average 46 gm., and contained from 0.94 mg. to 37.1 mg., average 37.1 mg.

[12] All war casualties. One, age 14 years has been omitted. The remainder varied from 19 to 55 years in age.

[13] Müller's technique was probably not very good. He found no iodine, or only traces, in 10 of the 65 "normal" glands examined. For our calculations, we have omitted all glands from persons under 17 years of age and all the data for glands which Müller's examination and analyses showed to be calcified. The series included 46 goiters, of which 9 are reported as containing "no" or only "traces" of iodine. Nevertheless, the average iodine content of these 46 goiters was 5.7 mg., as contrasted with 6.0 mg. for the normal glands.

[14] If one gland, weighing 553 gm. and containing 2.4 mg. of iodine be omitted, the value of the coefficient is more than 0.5.

[15] All data from persons under 15 years of age have been omitted.

[16] Of these 28 came from goitrous districts and 13 from a goiter-free region. The average weights were 28.2 gm. and 16.8 gm. and the average iodine contents were 5.43 mg. and 2.65 mg., respectively. **Those from the goitrous districts contained the more iodine.** Ten goiters contained from 0.9 to 21.3 mg. iodine. Only one of these contained less iodine than the lowest normal from a goiter-free district and none less than the lowest normal from the goitrous regions.

[17] All data from persons under 17 years of age have been omitted.

[18] Dog thyroids. Figures are for weight of thyroid and content in iodine per kilogram body weight.

Rietmann (87) have been omitted because the highest value for the total iodine in a normal thyroid was 1.6 mg. and, in 15 out of the 33 glands examined, he found no iodine at all or only traces. Also, all data for thyroids from persons known to have received iodine medication have been rejected. Nevertheless, in not a single series is there a negative correlation between the size of the glands and their iodine content. In many instances there is a high, and statistically significant, positive correlation. In only one series (Morgenstern), is the average iodine content of the goitrous glands less than the average iodine content of the normal glands, and this may be due to the large proportion (six out of twelve) of parenchymatous, nodular and calcified glands included among the goiters.

As a matter of fact, this conclusion that colloid goiters contain as much iodine as do normal thyroids may be derived from the work of Marine and Lenhart (70). In 23 normal glands, the iodine **concentration** per gram of dried tissue, varied from 1.3 mg. to 3.69 mg., with a median of 2.15 mg. and a mean of 2.17 mg. In 25 colloid glands, the corresponding values were 0.78 mg. to 3.91 mg., 1.77 mg. and 2.00 mg. The weights of the glands were not given, but the colloid glands were larger than the normal, so that, since the concentrations were much the same, the total amounts must have been greater in the colloid glands than in the normal glands. Marine and Lenhart stated:[3]

> This is probably accidental, for the reason that most of the cases are autopsy specimens, and many of them had received iodine medication.

It is unfortunate that Marine and Lenhart did not separate those, if any, that were known to have received iodine from those in which the presumption of such treatment depended entirely upon the iodine content of the gland.

Marine and Lenhart also reported that 19 normal sheep thyroids contained from 1.25 mg. to 4.61 mg., average 2.47 mg., of iodine per gram dried tissue, whereas three colloid glands contained 1.77 mg., 2.53 mg. and 3.69 mg., average 3.00 mg. Three "normal" dog thyroids were reported as containing 1.99 mg., 3.16 mg., and 4.72 mg., average 3.32 mg., whereas eight colloid glands contained from 0.85 mg. to 3.61 mg., average 1.99 mg., per gram of dried tissue. These findings are few and may be "accidental," but can scarcely be due to iodine medication.

In the last line of Table 1, there are summarized the figures reported by Marine and Williams (71) for the thyroids of dogs not previously submitted to operation or to medication. Obviously, it would be impossible to compare the absolute values for the iodine contents and weights of glands from animals that varied from 3.3 kg. to 34.5 kg. in body weight. Accordingly,

[3] Page 474.

the data for the weights of the thyroids and for their iodine contents are reported in terms of grams and milligrams, respectively, per kilogram of body weight. The data show a fairly good **positive** correlation. Certainly, there is not the negative correlation that the "iodine-lack" hypothesis demands.

We may, therefore, conclude that analyses of 969 thyroids, large and small, human, sheep and dog, by seventeen different observers, over a period of forty years, from Italy and Hungary to Japan and the United States, lend no support for the view that a lack of iodine was responsible for the enlargement. In fact, they show that there was no lack of iodine and that the cause of the enlargement must be sought in some other circumstance. In the case of a few goiters that really had a low iodine content, it is quite possible that the changes in the gland were so severe as to make iodine storage impossible or faulty, although, presumably, the diet contained quite normal amounts, and quite normal amounts reached the thyroid.

IV. GOITER IN ANIMALS UPON IODINE-POOR DIETS

Enlarged thyroids showing characteristic cytological changes, have been produced, but only on certain iodine-poor diets. Others appear to be ineffective (40). Moreover, in order to prevent such enlargements, it has been found necessary to add much more iodine to the diets than has been found in stock diets and even then the thyroids have been larger than in the control animals.

The data in Table 2 for the weight and iodine content of the thyroids of rats upon various diets are taken from the work of Levine, Remington and their associates (58, 59, 84, 86), which is, by far, the most extensive and most carefully controlled of all attempts to produce goiter by reducing the iodine intake.

Apparently, the stock diet originally employed by Levine, Remington and von Kollnitz (58, 59), was really a goitrogenic diet. At any rate, rats on this diet had larger thyroids than did rats of the same strain on a diet of commercial dog biscuit and these larger thyroids contained a lower concentration of iodine (entries 1, 9 and 11).

Supplementing diet GP with iodine in amounts not exceeding those found in the stock diet produced thyroids that contained a slightly higher concentration of iodine than did those on the stock diet, but the thyroids of the rats on diet GP plus these amounts of iodine were considerably larger than those on the stock diet (entries 1 and 5). To secure thyroids that were not, required a storage of iodine in the thyroid to three times the concentration and an intake of iodine three times the amount on the stock diet (entries 7 and 8).

TABLE 2. WEIGHT AND IODINE CONTENT OF THYROID GLANDS OF RATS UPON VARIOUS DIETS

Entry	Diet	Reference	Number of animals	Iodine intake per day μg.	Thyroid	
					Weight per 100 gm. body wt. mg.	I Content of dry tissue
						per cent
1	Stock[1]	58	39	0.74	12.9±0.25	0.0634
2	G.P.[2]	58	193	0.14	53.2±0.92	0.0083
3	G.P. KI	58	24	3.72	12.6±0.19	0.2671
4	G.P.[2]	59	20	0.14	50.6±2.6	0.0070
5	G.P. KI	59	10	0.59	17.5±0.41	0.0729
6	G.P. KI	59	10	1.02	16.4±0.49	0.1150
7	G.P. KI	59	10	1.93	14.9±0.44	0.1765
8	G.P. KI	59	10	3.72	13.0±0.36	0.2275
9	dog biscuit	84	—	—	8.8±0.4	0.200
10	342[3]	84	10	—	32.3±1.7	0.0051
11	dog biscuit	86	8	3.0	7.4±0.29	0.183
12	dog biscuit NaI	86	8	10.8	7.5±0.24	0.213
13	dog biscuit NaI	86	8	14.5	7.3±0.17	0.199
14	dog biscuit NaI[4]	86	8	9.6	8.0±0.32	0.322
15	dog biscuit NaI[4]	86	8	13.0	8.9±0.39	0.288
16	342[4]	86	8	—	25.2±1.8	0.024
17	342[4]	86	8	—	27.0±1.1	0.007
18	342[4]	86	8	—	25.9±1.6	—
19	342[4]	86	10	—	31.0±1.3	0.007
20	342[4] NaI	86	8	5.0–6.0	11.9±0.4	0.195
21	342[4] NaI	86	8	5.0–6.0	12.1±0.4	0.164

[1] Whole wheat, dried milk, meat scrap and NaCl.

[2] Steenbock rachitogenic diet with irradiated yeast.

[3] *Diet 342* consisted of wheat gluten, corn meal, $CaCO_3$, NaCl, and 2 per cent of dried liver. "On this diet, rats reach maturity and produce normal numbers of living young despite almost complete absence of iodine and colloid from the thyroid gland" (Ref. 84, page 232).

[4] Second generation on *diet 342*.

Similarly, rats previously on goitrogenic *diet 342*, even in the second generation responded to the feeding of quite large amounts of iodine **and dog biscuit** with normal, or even with excessive, concentrations of iodine (entries 14 and 15). Nevertheless, when kept on *diet 342*, plus 5 or 6 μg. of sodium iodide, about twice the amount contained in dog biscuit, the thy-

roids were about 1.5 times as heavy as those of normal rats (entries 9, 11, 20, and 21).

It is obvious that the requirement for a demonstration that lack of iodine may be the determining factor in the production of goiter—viz., that goiter should be produced on diets which, when supplemented with such quantities of iodine as are *found in normal diets (dog biscuit in this case)*, should produce glands as small and containing the same concentration of iodine as are obtained on normal diets—has not been met. Indeed, as Remington and Remington (86[4]) wrote:

> the technic (of Levine, Remington and von Kollnitz [(58, 59) I. G.] must now be considered as of a curative rather than a preventive nature.

This statement applies equally well to the later experiments of Remington (84) and of Remington and Remington (86), to the earlier work of Krause and Monroe (56) and of Thompson (98) and to the more recent experiments of Halverson, Shaw and Hart (37). Krause and Monroe obtained thyroids but little heavier (10 per cent) than the normal in rats on the Steenbock diet plus 25μg iodine per day, but such thyroids had from three to six times the concentration of iodine that was found in normal glands. Thompson did not weigh the glands nor determine their iodine content, but examined them histologically. She found that the addition of 20 μg potassium iodide per 100 gm. of Steenbock ration did not entirely prevent hyperplasia, but that the addition of 128 μg did. These additions would correspond to a supplementing of the daily iodine intake with about 2 μg and 12.8 μg, respectively.

In the experiments of Halverson, Shaw and Hart (37), there were but four animals in each group.

> Definite enlargement, redness and histological changes were noted in the thyroid glands of the rats on the basal ration and on the basal plus 0.5 μg. of iodine per rat per day. The addition of 1.0 μg. and 2.0 μg. of iodine per day to the basal ration largely corrected the glandular enlargement. The pathological changes in the thyroids were partially prevented by 1.0 μg. of iodine per day; however, 2.0 μg. resulted in **almost** [bold face I. G.] complete prevention of pathological change.

The iodine content of the basal ration is not stated, but it probably was quite low. The supplement of 2 μg. per rat per day is, assuming a total metabolism of 50 calories per day, at the rate of 120 μg. per 3000 calories. This is about as much as has been found in the urines of healthy persons in goiter-poor districts upon freely selected diets. Nevertheless, this was not sufficient to produce thyroids of normal size or appearance.

Remington (84) called attention to the decided goitrogenic action of the dried liver employed in his *diets 341*, *342*, and *343*. It would appear that

[4] Page 540.

not only these mixtures, but also the Steenbock diet and modifications thereof, employed in Remington's laboratory and in others, contained a positive goitrogenic agent which could be held in check by the administration of iodine and its accumulation in the thyroid in amounts exceeding the normal.

V. IODINE INTAKE AND EXCRETION IN DIFFERENT REGIONS

A. Analyses reported by proponents of the "iodine-lack" hypothesis

It is generally conceded that Chatin's methods of analysis were faulty. Therefore, no further attention will be given to his results. Our attention will be confined to the publications of the last twenty-five years.

The leading protagonists of the view that the environment is deficient in iodine in those regions in which goiter is endemic, have been von Fellenberg and Reith and their associates in Europe, McClendon in the United States, and Hercus and associates in New Zealand. There have been numerous other workers. They analyzed air, water, soils, foods and urines and reported that their iodine content was lower in localities in which goiter was prevalent than in those in which it was not. Largely because of the widespread idea, common among the laity in all regions in which goiter is endemic, that the drinking water is the cause of the goiters, this has received a great deal of attention.

1. Water

It is noteworthy that none of the chief proponents of the idea that a lack of iodine is the cause of goiter have controlled their analyses of water by the attempted recovery of **small** quantities of iodine added to a "synthetic" drinking water, made up from distilled water, pure salts and organic matter, and similar in composition to the drinking waters analyzed. In fact, most of them (von Fellenberg, McClendon and Hercus included) published no controls whatever. Others have published controls, but they contented themselves with addition of iodide to but one or two of the samples being analyzed, and then only in amounts far exceeding those originally present.

In Table 3, we have arranged a summary of some of the results reported by those who believed that their determination of the iodine content of water supported the "iodine-lack" hypothesis or whose work, as in the case of Höjer, has been so regarded by others (65). We have not included all of those reports in which the number of analyses was very small or in which the authors do not report their own analyses of water from both goitrous and non-goitrous regions. **However, no instances in which controls of any kind were published and which were believed by the authors to support the "iodine-lack" hypothesis have been omitted.**

The following comments upon the various entries in the table are offered:

a. Höjer did control two of his analyses (46). To 500 cc. of Lund tap-water containing 2.6 μg. of iodine, he added 1.27 μg. and found 3.5 μg. in the mixture. To another sample, also from Lund, containing 3.1 μg., he added 1.27 μg. and found 4.3 μg. These must be regarded as satisfactory controls **for these particular samples.** Höjer emphasized the necessity for extreme care in the determinations and the frequent failures, in spite of all precautions. **Moreover, he did not believe his results offered support for the "iodine-lack" hypothesis and he did not accept it** (48). His data have

TABLE 3. IODINE CONTENT OF DRINKING WATER AS REPORTED AS PREPONENTS OF THE "IODINE-LACK" HYPOTHESIS

Author	Date	Reference	Iodine μg. per liter	Controls
von Fellenberg	1923	25, 27, 28, 29	0.03–3.4	none
Jansen	1924	50	2.0–15.0	none
Hercus, *et al.*	1925	41	1.0–20.0	none
Höjer	1929	47	1.6–10.7	[a]
Mazzocco	1929	72	0.3–32.0	none
Cauer	1929	16	0.8–4.0	none
Adolph and Ch'en	1930	2	0.07–1.9	[b]
Straub	1930	96	0–530.0	none[c]
Bodnar and Straub	1930	13	0–1.0	none
Scheffer	1932	90	4.5	none[d]
Reith	1929	81, 83	1.0–96.0	[e]
Stacpoole	1938	94	1.1–6.0	none
McClendon	1923–29	65	0.1–7.3	[f]

been included in this table because they have been cited by McClendon (65) in support of this hypothesis.

b. Adolph and Ch'en added 7.5 and 75 μg. of iodine to 100 cc. of iodine-free water and recovered 87 per cent. The smaller of these additions is four times as great as the maximum found in any of the waters examined by them.

c. Straub found little or no iodine in the waters of many places that were free from goiter, and Bodnar and Straub (13) suggested that the deficiency was compensated for by other sources of iodine. The only analysis quoted by McClendon (65) is that of one iodine-poor water from a district in which goiter, previously only of sporadic occurrence, attained an incidence of 82 per cent among the school children within a year (13).

d. This is for the water of Pecs, Hungary, which had previously been analyzed by Straub and found to contain 0.3 μg. per liter; by von Fellen-

berg, 1.3 μg and 3.1 μg; and by Bleyer, 1.2 μg. The reports as to the incidence of goiter are equally, or more, diverse. Scheffer quotes Rutich (89) as authority for regarding Pecs as a goiter center: 13.7 per cent among children, and 8.8 per cent among adults in 1926, whereas Bodnar and Straub quote Gortvay (34) as having made a survey published in 1925, which showed it to be goiter-free. It is quite possible that the situation had changed within a year.[5]

e. The only controls as to the recovery of (total) iodine added to water published by Reith are to be found in his dissertation of 1929 (81). They follow:

	I found
1 liter Utrecht tap water, without addition	1.9 μg.
1 liter Utrecht tap water, 5 mg. sucrose and 20 μg. iodide	20.5 μg.
1 liter Boskoop tap water, Sample A, without addition	10.8 μg.
+20 μg. iodide	32.2 μg.
1 liter Boskoop tap water, Sample B, without addition	9.1 μg.
+20 μg. iodide	28.7 μg.

Four years later, Reith (83) published a method for the fractionation of the iodine content of water. We are not concerned with the details, but the following data are of interest:

Locality	Barendrecht		Gouda		Zoutphen	
	Without Addition	100 μg. iodide Added	Without Addition	100 μg. iodide added	Without Addition	100 μg. iodide added
	μg.	μg.	μg.	μg.	μg.	μg.
Sum of all fractions, per 500 ml.	48	134	33.3	109	22	86
Previously determined Total iodine (1929)	51		29.4		21	
Total iodine (1930)	43		35.0		22	

It will be noted that the sums agree very well with the previously determined values for total iodine. Nevertheless, iodide, added in quantities from two to four times as great as the total iodine originally present, was incompletely recovered; the increase in the amount found being only 86.7 per cent and 64 per cent of that added.

f. None of the earlier papers by McClendon and his associates contains

[5] See preceding paragraph and page.

any evidence of control analysis of water. Recently, Bratton and McClendon (15) published a new method for the determination of iodine in water and other materials. For this, only 200 cc. of water are taken and the two controls published are quite satisfactory as shown below:

Sample	I	Added	Found
	μg.	μg.	μg.
200 cc. Minneapolis tap water	0.43	0.54	0.98
200 cc. La Grange tap water	0.50	0.55	1.13

In a subsequent publication, McClendon and Foster (66) reported the values, given above for 200 cc. water, as for a liter. Neither agrees with the value, 0.8 gm. per liter, given in McClendon's reviews (64, 65), which, according to a letter from him, is based upon hundreds of analyses.

Compared with the amount of iodine obtained from the food or excreted in the urine, that furnished by even 1.5 liters of water per day is usually insignificant. Only Reith and his associates consider the water an important source of iodine. Other writers, beginning with von Fellenberg (31) in 1933, have regarded the iodine content of the water as significant only as it may serve as an indication of the readily available iodine of the soil and, presumably, of the iodine content of the produce of that soil.

2. Soils and foods

There are hundreds of determinations of the iodine content of the soil to be found in the literature and these include a few reports in which there appears to be no correlation between the iodine content of the water and the occurrence of goiter, although there is such a correlation between lack of iodine in the soil and the occurrence of goiter. However, none of the reports purporting to demonstrate the latter, regardless of any relation between water and goiter, are accompanied by any control analysis.

We do not eat soil, but plant and animal products. The literature contains the results of the analyses of hundreds of samples of foods. Very few of those purporting to show that there is a correlation between the incidence of goiter and a low content of iodine in the food are accompanied by suitable controls. Apparently, von Fellenberg published no controls at all; neither did Hercus and his associates. There are a few controls to be found in the papers by McClendon and associates. Thus we find (67) that of 200 μg. of iodide added to 50 gm. of iodine-free starch, 194 μg. were recovered. However, the highest concentration of iodine in **any** vegetable analyzed by this method was 333 μg. per 1000 gm. of dry potatoes. A proper control would have been the recovery of 17 μg. or less, of iodide added to 50 gm. of starch or of 100 or 200 μg. of iodide added to 1000 gm. of starch. Using a slightly different procedure, McClendon and Remington (67) found 100

gm. dry potatoes to contain 34μg. of iodine. Another sample, to which 100 μg. of iodide were added yielded 129 μg. A proper control would have been the recovery of 34 μg. or less, added to the potatoes.

That the methods of McClendon and Remington are not accurate to within 35 or 50 per cent is indicated by the statement of Baumann and Metzger (11). Previously, they had made four determinations upon a vegetable preparation, using ashing at 400°C to 500°C, and had obtained values of 0.17 mg., 0.18 mg., 0.23 mg. and 0.25 mg. per kilo.

Through the courtesy of the South Carolina Food Commission, four determinations in a similar preparation were made for us with equally great variation.

Adolph and Ch'en (2) added 7.5 μg. iodide to each of two portions of 50 gm. of wheat containing about 0.43 μg. iodine. The amounts found were 6.67 μg. and 6.69 μg. Since the highest content of iodine found in any sample of wheat was 22 μg. per kilogram, a proper control would have been the addition of 0.5 μg. iodide. Even as it was, with added iodide more than 17 times as great as that originally present, the recovery was only 84 per cent.

Reith (81, 82) added varying amounts of iodide to samples of flour and of milk and found that even with additions of from four to twenty times as great as the amounts originally present, the recoveries were only about 85 per cent.

There is not to be found in any of the reports by the proponents of the "iodine-lack" hypothesis, a single control in which a quantity of iodide comparable to that originally present was added.

Anyone with any experience in the analysis of foods knows that their content of any particular constituent may be rather variable. Therefore, the analyses of chance samples, as employed by von Fellenberg, McClendon, Reith and others, can scarcely be expected to give much information regarding the iodine intake throughout the year.

The figures given below are of interest in this connection. They represent the iodine content, in micrograms per kilogram, of **different varieties of the same vegetable, grown upon the same soil, and at the same time** (33).

Soil	Vegetable	Variety A	Variety B	Variety C
1	Beet leaves	369	1030	
1	Beet roots	180	308	
2	Broccoli	521	3502	
3	Cabbage	1208	2163	
4	Cabbage	153	223	667
5	Potatoes	160	1045	

These differences are at least as great as those reported by anyone as

existing between the iodine contents of vegetables, or other foods, in different regions.

3. Urine and feces

Recognition of the practical impossibility of ascertaining the iodine intake from an analysis of foods seems to have led various workers to an examination of the urine. They assumed that nearly all of the ingested iodine leaves the body in the urine, or, at least, that the amount excreted through this channel is, in an adult, presumably in iodine equilibrium, a good index of the iodine intake. However, there are few determinations of the iodine content of feces in the literature and such as there are do not substantiate this.

It is true that Scheffer (91) in eleven experiments of five days' duration with a daily intake of from 54 μg. to 131 μg. of iodine, found only from 2.2 μg. to 9.9 μg. in the feces. However, it is noteworthy that in all but two of these experiments, the urine and feces together accounted for only from 3 per cent to 52 per cent of the total intake and that in the one case in which 9.9 μg. of iodine appeared in the feces, there was only 11.6 μg. in the urine.

Von Fellenberg (26) maintained himself upon diets of nearly the same iodine content, about 75 μg., but in which the chief source of the iodine was varied and found that when this was potassium iodide or cod liver oil, about 10 per cent appeared in the feces; when it was sardines, about 20 per cent; but when the greater part of the iodine was furnished by 330 gm. of watercress per day, it was 22 per cent on the second day and 83 per cent on the third. (The stools were soft and increased in weight on both of these days.)

With a constant diet and an intake of 156 μg. a day, Cole and Curtis (19) found in the feces of successive three-day periods, 38 μg., 19 μg., 30 μg., 31 μg., and 16 μg. of iodine per day. In another subject, also on a constant diet, but with an intake of 56 μg., they found the daily fecal excretion of iodine to be 8 μg., 6 μg., 9 μg., 10 μg., and 12 μg. in successive three-day periods.

With a constant diet and an intake of 101 μg. and 95 μg. in two, three-day periods, Puppel and Curtis (80) found the excretion in the urine to be 133 μg. and 110 μg. per day; and in the feces, 23 μg. and 44 μg. In another individual, also upon a supposedly constant diet, supplying 77 μg., 74 μg., and 61 μg. iodine per day, the excretion in the urine was 158 μg., 158 μg., and 157 μg. and 41 μg., 30 μg. and 32 μg. in the feces, per day, in three successive three-day periods.

The man upon whom the latter observations were made then received "iodized milk"—milk obtained from a herd fed supplemental amounts of

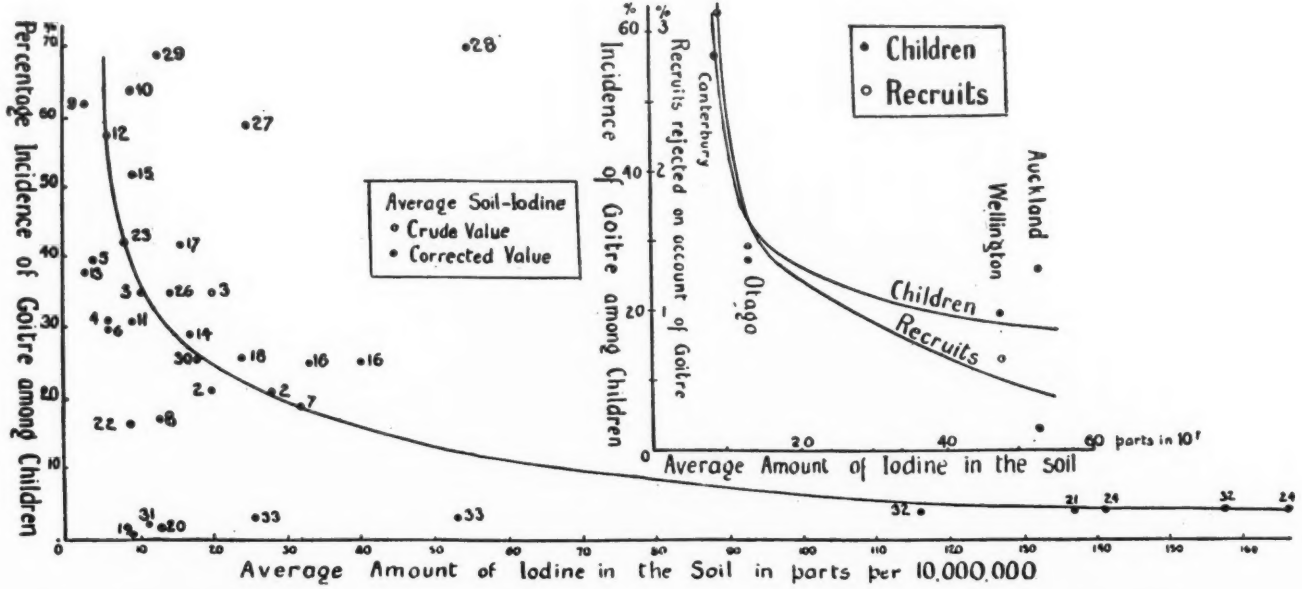

CHART I. Curves showing the relationship between the average amount of the iodine in the soils and the regional incidence of goiter among school-children and military recruits in New Zealand. The figures by dots denote the districts indicated in Table 5.

iodine. The intake rose to 1.61 mg. and 1.70 mg. and the feces contained 102 μg. and 97 μg. per day. With much larger quantities of iodine, administered as potassium iodide, so that the total intake was 9.1 mg., the amount found in the feces was only 51 μg. and 66 μg. Even with as much as 18.1 mg. of iodine, as potassium iodide, the amount in the feces was only 111 μg.

Why the iodine in "iodized milk" should not have been absorbed or why it should have been excreted in the feces in such amounts, is not clear. However, it is interesting to recall, in this connection, that Greenbaum and Raiziss (35) had previously found that, of 0.6 gm. iodine per kg. of body weight, administered by mouth to rabbits in the form of calcium iodide, some 30 per cent to 40 per cent appeared in the feces, whereas when the same amount was given as sodium or potassium iodide, practically all of it was found in the urine.

These results of von Fellenberg, of Cole and Curtis, and of Puppel and Curtis certainly do not indicate that the excretion of iodine in the feces is either so small or so constant as to be negligible in a consideration of the significance of differences in the excretion of iodine in the urine.

Even if the possibility of variation in the excretion in the feces be excluded or if all of the iodine in the feces be regarded as unabsorbed, the results reported for the excretion of iodine in the urine do not lend support to the "iodine-lack" hypothesis. None of the authors who consider their work as indicating such a difference in the iodine content of the urine in goitrous and non-goitrous areas seem to have made any control analyses. Triebart (99), whose work is cited by McClendon (65) in support of the iodine-lack hypothesis, did perform control analyses and reported satisfactory recoveries. However, his data, except for those obtained from a few workers in the laboratory in Batavia, are for the iodine content per liter of **mixed** urines obtained from people in non-goitrous and in goitrous areas. The latter values were lower, but there was considerable overlapping. Strangely enough, the urines of goitrous individuals had a lower iodine content than those of healthy persons living in the same area. Triebart did not believe that his result supported the "iodine-lack" hypothesis. In my own opinion, the lack of information as to the time represented by a liter of urine deprives them of any significance whatever.

B. Validity of comparitive determinations, even if absolute values are erroneous

Granted that the methods have not been properly controlled, that they really are very faulty, may not a series of determinations by the same analysts show significant differences? In the author's view, a critical ex-

amination of the results reported fails to yield even this support for the "iodine-lack" hypothesis.

In 1923, Hercus, Benson and Carter (41) published the results of a large number of analyses of soils from various areas in New Zealand. They present, as evidence for the "iodine-lack" hypothesis, Chart I, in which the average concentration of iodine in the soil in different districts is plotted as abscissae; the percentage incidence of goiter among school children as ordinates. Three points, *24*, *32* and *33* have been corrected for anomalous high figures and appear in the chart in both the corrected and uncorrected forms. It is obvious that the lower part of the curve, that representing an incidence of less than 19 per cent of goiter, depends entirely upon points *21*, *24* and *32*. To draw a curve through these points it is necessary to neglect points *19*, *20*, *31* and *33*. There is no reason for this. As a matter of fact, the points are best described by the two lines: soil iodine = 20 parts per million, and the incidence of goiter = 35 per cent. There is no evidence of any correlation between low content of iodine in the soil and a high incidence of goiter.

A few years later, Hercus and Roberts (43) published the results of a smaller series of analyses of urine from goitrous and non-goitrous areas. Only the minimum, maximum and average values were given. It occurred to me that the differences might be due to a very small number of unusually high values. I asked for the original data and received the following reply:

> Professor Hercus has referred your letter of July 7*th*. to me. We do not possess records of the laboratory investigations on goitre performed here prior to 1928. I have read the Hercus and Roberts paper critically in relation to our present knowledge and experience and consider the demonstration of a relation between goitre and urinary iodine excretion therein presented to be unsatisfactory in the following respects:—
>
> 1. No specimens were obtained from a truly non-goitrous district and the specimens classified as non-goitrous include those from subjects without goitre consuming the same diet as subjects classified as goitrous.
>
> 2. The method of iodine analysis as practiced at that time gave uncertain, often bizarre, results. The tendency was for the analyst to discard high results from goitrous regions and low results from supposedly non-goitrous regions as being anomalous. The logical significance of the results was thereby destroyed and the question of the statistical significance is not important.
>
> Investigations into urinary iodine excretion were carried out here by more precise methods after 1934. Some of the results were reported in the paper of which a reprint is enclosed (see pages 187–188). The typewritten extract from the New Zealand Medical Research Council's Report, 1939, gives the result of all determinations made in these later investigations, and shows that the same relation obtains between goitre incidence and urinary iodine excretion in New Zealand as in other parts of the world.
>
> (signed) H. D. Purves

The reprint referred to in this letter is that of a paper in the *Journal of Hygiene* (42). **There is, therein, no mention of any controls.** The data

do show a difference that is statistically significant in spite of a considerable degree of overlapping. But it is a difference between the iodine content of certain **24 hour** urines obtained in New Zealand and those obtained in other countries. The possibility of seasonal variation has not been considered, although Hercus and Roberts (43) had previously reported equally as great, or greater, variations in the excretion of iodine by the same individuals in **weekly** periods at different seasons, or even in two successive weeks. It would appear, therefore, that the results reported by Hercus and Purves for **24 hour** urines do not have the significance that they attach to them.

Three years before the paper by Hercus and Roberts had appeared, von Fellenberg (29) published the results of the analyses of a smaller number of urines:

7 from a goiter-free region	28 μg. to 108 μg., average 64 μg.
11 from a goitrous region	4 μg. to 29 μg., average 20 μg.
12 from a goitrous region	5 μg. to 28 μg., average 17 μg.

These determinations were made on night urines from periods of unstated length, but calculated to 24 hours. Von Fellenberg wrote:

> Die Berechtigung, aus der nächtlichen Jodausscheidung auf die in 24 Stunden erfolgte zu schliessen, soll in einer späteren Arbeit nachgewiesen werden.

That later paper (30) contains **one** experiment upon himself on his usual diet. The figures presented contradict von Fellenberg's statement that the hourly excretion during the night is the same as during the day. The excretion during the 8.5 night hours was at the rate of 0.86 μg. per hour; that for the previous 15.5 hours was at the rate of 0.75 μg. per hour. Evidently a difference of over 14 per cent was considered insignificant. Von Fellenberg goes on to state:

> Dieser Befund steht in einem gewissen Widerspruch mit einem Resultat welches ich früher beim Hungern hatte. Dort war nachts bedeutend weniger Jod ausgeschieden als am Tage. Jener Versuch ist bei einer stärkeren Jodbelastung des Korpers ausgeführt worden. Man hatte in den Vorperiode jodreichere Nahrung eingenommen und eine leichte abspaltbare Jodreserve eingelegt.

However, when we turn to that earlier paper (26) we find the following:

First fasting day	6 a.m.–6 p.m.	12.8 μg.
	6 p.m.–6 a.m.	5.6 μg.
Second fasting day	6 a.m.–6 p.m.	23.0 μg.
	6 p.m.–6 a.m.	5.3 μg.
On usual diet (30)	24 hours	18.9 μg.

It may be noted that the iodine excretion in the urine on the first day after the iodine-rich food was **not** higher than when on his usual diet, three

years later. Moreover, it is not clear why the excretion should have doubled during the second day of the fast.

Actually, in the same paper in which he attempted to justify the use of night urines for establishing the daily excretion, von Fellenberg reported that emotional strain increased the iodine excretion in the urine. The observation was made on an eight-year old girl, who at noon, on the last day of the period of observation, received an invitation to an excursion on the following day. She was not told that she could go until that evening. The following data for the iodine in the urine were presented.

night (calculated to 12 hours)	13.7 μg.
day (calculated to 12 hours)	17.3 μg.
night (calculated to 12 hours)	10.8 μg.
day (calculated to 12 hours)	16.0 μg.
night (calculated to 12 hours)	9.6 μg.
day ("In Spannung und Erwartung")	20.3 μg.
night ("In Spannung und Erwartung")	33.0 μg.

It will be noted that this eight-year old girl, before the exciting invitation had been received, excreted more iodine in the urine than did von Fellenberg, either on his usual diet, or when fasting after a period of "Jodbelastung." It will also be noted that the excretion during the night hours was uniformly (before the excitement) at a lower rate than during the day.

In 1932, the Netherlands government published a 500-page report on the goiter problem in that country (52). Curiously enough, goiter was regarded as extremely rare until 1917, when it was found that a large number of recruits, especially those from the southern and eastern parts of the country, could not wear the uniform because the collars were too small. Equally curious is the high iodine content of the water.

In the English summary of this report,[6] we may read:

> From the analysis of samples of milk, grass, potatoes, vegetables, corn, etc. (a total of 120 analyses), it may be taken that these products in the towns and provinces where there is little goiter are somewhat richer in iodine than in areas with much goiter. These variations are, however, not so important as those in the drinking water. [This is in contradiction to all other reports, I. G.]
>
> The study of the discharge of iodine has also given similar results. The examination of samples of urine from Breda (much goiter) and Zutphen (little goiter) numbering together 120 samples, gave as the result, that the discharge with the urine in the two towns averaged 29 μg. and 51 μg. iodine, respectively. In Kampen and Barendrecht, towns, the one with much goiter and the other with none, 30 samples of urine were taken later, which showed a discharge of 47 μg. and 186 μg. respectively.

In the first place, it will be noticed that the urinary excretion of iodine in Kampen, with much goiter, had an average value of 47 μg., whereas in Zutphen, with little goiter, it was 51 μg. Why the Commission compared

[6] Ref. 52, page 275.

Zutphen with Breda and Kampen with Barendrecht and not Kampen with Zutphen is not apparent from this report.

Reference to the actual data upon which these averages were based discloses the following: The 120 samples represent a six-day period of observation upon five man and five women in each of the two towns. The 120 samples, therefore, represent only twenty individuals, regarding whom there is no information on either age or weight, except that in Zutphen they were inmates of a home for the aged and in Breda, monks in a monastery and teaching sisters in a school. Data for the individual days are not given so that there is no information regarding variations from day to day. If one calculates the averages separately for men and women, the differences are 21 ± S.D. 9.5 for the women and 20 ± S.D. 26 for the men. Such results cannot be regarded as having any significance.

The other pair of averages is derived from samples made up of three night urines from each of six persons, from which a composite supposed to represent 24 hours was made. There are no thirty samples, only twelve. There is no information as to body weight. The available data are given below:

	Barendrecht				Kampen		
	Age years	Per 24 hours μg.	Per liter μg.		Age years	Per 24 hours μg.	Per liter μg.
Male	26	202	114	Male	23	40	45
Male	38	209	57	Male	44	29	16
Male	49	216	174	Female	35	120	110
Female	41	151	146	Female	44	41	18
Female	48	87	49	Female	25	33	39
Female	46	252	178	Female	25	19	18
Average		186				47	

It will be noticed that one man in Barendrecht seems to have excreted nearly four liters of urine per day, whereas one man and one woman in Kampen seem to have excreted less than a liter per day. It is impossible to regard these data as accurately representing the daily urinary excretion of iodine by these individuals or as reflecting their customary iodine intake.

C. Reports regarded by the authors thereof as opposed to the hypothesis, or as equivocal

Up to this point, we have considered the reports regarding the iodine content of the environment, food and excretion that have been used to support the "iodine-lack" hypothesis. We now turn to those papers that, in the opinion of their authors, contradict the hypothesis or contain equivo-

cal observations. Only such reports as include analyses, by the same workers, of material from goitrous and non-goitrous regions, will be included in this section. In these we find more evidence of control analyses than among the publications by proponents of this hypothesis.

A few years after the appearance of the first paper by Hercus and associates, there was another investigation in New Zealand by Shore and Andrew (92). They used a modification of von Fellenberg's colorimetric method. In a separate publication, Andrew (5) presented the results of some control analyses in which from 4 μg. to 180 μg. of iodine were added to from 2 gm. to 3.5 gm. of soil. The recoveries varied from 60 per cent to 70 per cent, regardless of the amount of iodine added.

Andrew (5) also studied the recovery of iodine added to water. It was only 50 per cent to 60 per cent, but no data were presented.

Shore and Andrew assumed a uniform recovery of 67 per cent. From their report,[7] I quote:

> It is obvious that no correlation exists between the amount of iodine in the potable water and the incidence of goiter.[8]
>
> Generally speaking, where the iodine content of the soil is high, the incidence of goiter is low, and where the former is low, the latter is high. There are, however, certain anomalies which at present cannot be accounted for.

A few years later, they (93) reinvestigated the situation with particular reference to one of the "anomalies" discovered in their previous work. They confined their attention to three districts: Palmerston North, with low iodine and high goiter; New Plymouth, with high iodine and low goiter; and Thames, with low iodine and low goiter. They found that, in the five years since their former census, there had been a tremendous increase in the incidence of goiter in New Plymouth, so that, although there had been a smaller increase in the other districts, there was now more goiter in this former low-goiter area than in either of the other two districts.

A summary of the data is given below:

	Iodine in soil, per 10^7		Goiter among school children			
			1928		1933	
	1928	1933	M per cent	F per cent	M per cent	F per cent
Palmerston North	47	45	35	39	67	72
Thames	74	126	8	9	23	31
New Plymouth	854	1005	6	7	82	87

[7] Ref. 92, page 52.

[8] *Idem.*, page 65.

They also analyzed a number of urines. The figures represent micrograms per liter.

	Thames	Palmerston North	New Plymouth
	μg.	μg.	μg.
Children (23 each)	16–222	12–160	24–360
Average	61	41	77
Corrected for anomalous values	36	36	57
Adult, night urines (26 each)	16–128	16–192	28–164
Average	57	49	70
Adult, night urines (15 each)	16–80	20–80	22–80
Average	40	41	47

From their summary, I quote:

3. In 1928, an inverse relationship apparently did exist.
4. The results now reported in no way support this hypothesis.
5. Actually the amount of goitre encountered in a district with high iodine content available is in excess of the amount present in a district with low iodine available.
6. The average amount of iodine contained in vegetables from the different areas is remarkably similar.

We now turn to a group of English workers, headed by J. B. Orr. Their first publication was in 1927 (77). This contained no mention of control analyses. The authors did report that they found it difficult to extract all the iodine from water that yielded a precipitate of calcium carbonate on the addition of alkali. The few analyses they reported showed no relation between the iodine content of the water and the incidence of goiter.

In Orr's next publication on this subject in 1931 (76), there are these statements:[9]

With regard to the accuracy of the method as a whole, we found that we did not get complete recovery of known added quantities of iodine . . . .

On the other hand, although estimations of iodine by this method cannot be considered as giving absolute figures, results on similar materials by any one worker appear to be comparable. The order of magnitude of the amounts estimated, where known differences occur, appears to be a fairly accurate representation of the differences, but on a somewhat lower level.

There is not a word as to how much iodine was added, nor as to how great the losses were. Accepting his figures at their face value, I quote from the report:

The results must, however, be considered as inconclusive. All that can be said is that there is an indication in the summary . . . that the iodine supply, as judged from the analyses of milk, eggs, and cabbage is higher in the Scottish area which is known to be goitre-free than in the English counties where goitre is, to a greater or less extent, endemic. On the other hand, there is no indication whatever of any definite difference

[9] Ref. 76, page 677.

between those areas in England which were reported to have a low goitre incidence and those reported to have a high goitre incidence.

The next report appeared in 1936 (20). The analytical methods used were those of Harvey, described in a separate publication (39). In that, there is not one control upon water. There are control analyses upon milk and a few upon hay.

The results obtained in the investigation may be summarized as follows:

12 Villages	In Somerset	In Suffolk
Incidence of goiter	42 per cent to 76 per cent; av. 56 per cent	0 per cent to 7 per cent; av. 3 per cent
Water, per liter, 21 samples, three excluded	1.2 μg. to 4.3 μg.; av. 2.9 μg.	
Water, 19 samples, one excluded		2.1 μg. to 21.0 μg. av. 8.2 μg.
Winter, milk, per 100 cc.	0.4 μg. to 6.2 μg.; av. 3.15 μg.	0.72 μg. to 13.4 μg.; av. 3.78 μg.
Summer, milk, per 100 cc.	0.44 μg. to 1.57 μg.; av. 0.83 μg.	0.43 μg. to 1.33 μg.; av. 0.76 μg.
Pastures, per 100 gm. dry	19 μg. to 45 μg.; av. 28 μg.	13 μg. to 50 μg.; av. 25 μg.

From the report, I quote:

> The results are discussed and it is concluded that, whilst they demonstrate once more the recognized relationship of environmental deficiency of iodine to the incidence of goitre, they do not give conclusive proof that such deficiency is the sole cause of the abnormality of the thyroid in the district investigated. The possible role of variation in the availability of soil iodine to herbage and hence to the animal population as a complicating factor is briefly discussed in relation to recent work by other investigators.

In the author's opinion, not only do these data afford no "conclusive proof that such a deficiency is the sole cause of goitre," but they do not "demonstrate once more the recognized relationship of environmental deficiency of iodine to the incidence of goitre." In fact, they seem to demonstrate the very opposite. If the pastures be considered as representative of the vegetable crops raised locally and the milk of the corresponding animal products, the only difference in the iodine intake by the two groups of children was due to the water. **Certainly, this was the only difference observed.** Even if a child drank a liter of water per day, the difference in iodine intake in the two counties would be, on an average, 5 μg per day. There are no data for the total intake, but the report states

> The daily iodine requirement of a child is believed to be between 25 and 50 μg.

It would appear, therefore, that the differences in the iodine contents of the waters were only a small part of daily intake.

Moreover, there were several places in Somerset that had as high a con-

centration of iodine in the water as some of those in Suffolk. One of these, Creech St. Michael, with 46 per cent goiter, furnished two samples of water containing 14.8 μg and 26.0 μg per liter respectively. (Both were excluded from the average.) In fact, all but three of the eighteen samples from Somerset contained at least as much iodine per liter as did one from Suffolk and eleven (or eight, if the highest three be excluded) from places in which half the children had goiters, had as high a concentration of iodine as had three waters from Suffolk, from villages in which the incidence was only three or five per cent. It is difficult to understand how such results can be said to "demonstrate once more the recognized relationship of environmental deficiency of iodine to the incidence of goitre."

Using several methods for the determination of the iodine content of water and soil, McCarrison and his associates (63) found no correlation between these and the incidence of goiter in India. Neither did Adlercreutz in Finland (1), nor Lunde (61) in Norway, find any such relation between the iodine in the water and the incidence of goiter. In fact, the latter found a high incidence of goiter in certain localities in which the water contained 26 μg. and 32 μg. per liter. In other places the iodine content of the water was much less, only 0.1 μg. to 2 μg. per liter; yet the iodine content of the urine was much the same, 11.3 μg. to 35.0 μg. per 100 cc., or 132 μg. to 435 μg. per day. This is higher than was found by Lunde in other goiter districts in Norway (60) and, indeed, is higher than is reported from anywhere else except, possibly, by the Netherlands Commission (see page 726) and that for only **one goiter-poor** community.

Returning to von Fellenberg's publications, we find that in the earlier ones, he emphasized the differences in the iodine content of the water, soil and urine in two localities in Switzerland; Signau, in which the incidence of goiter was said to be high, and Le Chaux de Fonds, which was said to be goiter-free. Within a few years (in 1928), Stiner (95) called attention to the fact that there was no such difference if one judged by the observations made on recruits in 1924 and 1925. The goiterous individuals in the two groups numbered 28 and 21 per cent, respectively.

As a matter of fact, von Fellenberg, himself, after an investigation of the situation in another Swiss locality wrote, in 1938 (32):[10]

> Wir kommen also zu dem Schluss, dass ein deutliche Zusammenhang zwischen den Jodgehalt der Nahrung und dem Auftreten von Kropf und Kretinismus sich in der Gemeinde Blumenstein nicht nachwiesen lässt, dass aber ein die Kropfnoxe verstärkender Einfluss der hygienischen Beschaffenheit des Trinkwassers nicht ausgeschlossen ist.

With this confession by one of the chief protagonists of the "iodine-lack" hypothesis, we may take our leave of the evidence purporting to show that

[10] Page 97.

there is a difference in the iodine intake in various communities and that this difference is responsible for the variation in the incidence of goiter.

The difference in goiter incidence in much of the United States can scarcely be due to a difference in the iodine content of local supplies. These make but a slight contribution to the feeding of our large cities. If Cleveland, Chicago and Minneapolis have more goiter than do New York, Boston and Philadelphia, it cannot be due to local food, for the inhabitants of these cities eat very little of that. Most of the food in these cities comes from the same sources or is derived from animals fed the same concentrated feeding stuffs or from plants raised upon soils enriched with the same fertilizers. The difference in the iodine content of the drinking water supplied these cities is entirely too small to be significant. According to Hale, quoted by McClendon (65), the water supply of New York City contains 1.1 μg., 1.3 μg., and 2.5 μg. per kg. for the Catskill, Croton, and Long Island supplies, respectively. The former two are the principal sources. A liter of either of these per day would supply only 1.1 μg. or 1.3 μg. of iodine, which is negligible, for the daily requirement has never been placed at less than 15 μg. and is usually regarded as several times that value.

IV. THE PROPHYLACTIC USE OF IODIDES

If endemic goiter is a deficiency disease, due to a lack of iodine, the prophylactic use of iodides should have abolished it. That has not been the case. All that has been observed is that the new cases are fewer and that the goiters are smaller.

In Cleveland, in 1935 (54), even among the children from families in which iodized salt had been used regularly for three years, or more, immediately preceding the survey, there was still seven per cent of goiter, as compared with 31 per cent in 1924, before the regular use of iodized salt had begun. A decline that was fully as great as this, from 40 per cent in 1924 to 8.2 per cent in 1935, was observed in Michigan **regardless of whether or not iodized salt had been used** (21). Even among those who **never** used iodized salt, in Macomb County, the change was from 26.0 per cent to 7.7 per cent; in Midland County, from 32.7 per cent to 14.6 per cent; and in Houghton County, from 64.4 per cent to 25 per cent; diminutions representing 70 per cent, 55 per cent and 51 per cent, respectively, of the original incidences—**all among children from families in which iodized salt had never been used.** There is no comparable group from Cleveland in Kimball's report, but among those not using iodized salt during the last three years, the incidence was what it had been in 1942; viz.: 31 per cent.

Kimball ascribes the persistence of 7 per cent of goiter, in spite of twelve years of prophylaxis with iodized salt to two manufacturers

who could not make up their minds on the value of this method of goiter prevention and consequently put little or no iodine in their iodized salt. . . . On repeated analysis in 1936, of the various brands of iodized salt sold in Cleveland, we found several brands of iodized salt that contained only one-third the amount of iodine stated on the label, and one brand sold by a large chain store which contained no iodine. The same two manufacturers in the Cleveland district are responsible . . . the average of thirteen brands for Cleveland was only 0.01 per cent, or half of what was stated on the label.

The iodized salt used in Cleveland and in Michigan was supposed to contain 0.023 per cent of sodium iodide. An intake of ten gm. of salt per day would have furnished 1.05 mg. of iodine per day. This is at least ten times as much as has been reported by any one for the customary intake, or excretion, in goiter-free regions. Even if the salt contained only "one-third the amount of iodine stated on the label," an intake of 10 gm. per day would still have supplied 0.35 mg. of iodine per day. This is still far greater than has been reported as the customary intake, or excretion; in any goiter-free region. Moreover, based upon the Swiss experience, to be discussed later, Eggenberger (22) concluded that a daily intake of 2 micrograms of iodine per kilogram throughout life was enough to protect against any dangers of goiter: even in such conditions as puberty, pregnancy, infections and intoxications. This amount of iodine would be 0.14 mg. per person of 70 kg. body weight, and would be furnished if only 7 per cent of the salt intake were of the fully iodized salt, or if it were 21 per cent of the poorly iodized salt, and all the rest of the salt contained no iodine whatever.

Therefore, Kimball's explanation cannot be accepted unless it be assumed that the **one** brand of salt that contained no iodine at all was the only one used by most of the families concerned in his survey.

It is possible that the difference in the results obtained in Cleveland and in Michigan were due to variations, of unknown cause, in the virulence of the disease, such as have been recorded repeatedly (36, 45[11]). The twelve years from 1924 to 1935 may have represented a period of decline in Michigan and a period of increase, prevented by relatively large amounts of iodine from exerting its full effect, in Cleveland.

In Switzerland, only five or ten milligrams of iodine have been added per kilogram of salt. Ten grams of this would furnish 50 or 100 micrograms. According to Eggenberger and Messerli (23), the former of these was not enough to prevent the occurrence of goiter in Appenzell, although 100 micrograms was sufficient. These were amounts added to those contained in the food and, therefore, the total intake approached, if it did not actually exceed, the **highest** amounts recorded for the normal intakes or excretions in goiter-free regions.

[11] Volume 2, page 121.

In Poland, the use of iodized salt containing from 3 mg. to 7 mg. of potassium iodide per kilogram and, therefore, furnishing from 23 μg. to 54 μg. of iodine per ten grams, was followed by a reduction in the incidence of goiter (100). These amounts are really small and are such as might be found in an ordinary diet. However, there have been spontaneous decreases in the prevalence of goiter that were equally pronounced. Possibly the latest to be recorded is to be found in the report by Berard and Dumet (12) of a great diminution in the intensity of goiter throughout all of the goiter districts in France during the thirty years from 1897 to 1927, although there was no organized propaganda for the use of iodides. These thirty years included the period of these observations in Poland and of Hunziker's experiments in Switzerland (see below).

Of all the reported successes with the prophylactic use of iodine, only the original investigation by Marine and Kimball (69) and one by Hunziker (49) seem to have been controlled with a group not receiving iodine. There can be no question of the reality of the differences in the incidence of goiter in the two groups, but there may well be some question as to the source of the difference. With a population as heterogeneous as that of Akron, the possible influences of dietary habits, hygienic conditions, etc., should not be lightly neglected. Finally, it is possible that the period of observation was one of increased virulence of the disease, held in check in one group by the use of iodide.

That may also have been the case in Hunziker's experiment in Adliswill, Switzerland, in 1920–1921 (49). About one-half of the school children received one milligram of potassium iodide weekly, for 40 weeks. At the end of this period, the average size of the thyroids in this group was less than that of the thyroids of the untreated children either in 1920 or 1921. Although there are no data for the changes in size of thyroids in the same children, a beneficial effect of the iodide may be granted because there was a greater proportional reduction in the asymmetry of the thyroid and in the number and size of nodules therein than in the untreated group. However, during this period, the average size of the thyroids of the untreated children in the same age groups increased as shown below:

	1920		1921	
	Age years	Size of thyroid cm^2	Age years	Size of thyroid cm^2
Boys	10.3	16.6	10.0	17.0
Girls	10.2	17.0	10.2	17.7

In some other countries, the prophylactic use of iodides has not been so

successful as has been claimed to be the case in the United States, Switzerland and Poland.

From New Zealand, Hercus, Benson and Carter, prominent proponents of the "iodine-lack" hypothesis, wrote in 1925 (41):

> The results of one year's treatment were encouraging, but were in no way comparable to those of Marine.

Of 162 untreated children, of both sexes, showing no enlargement of the thyroid at the beginning of the year, 89 or 55 per cent had perceptible goiters at its close: but so did 38, or 39 per cent of the 96 children who received iodine. After three years of prophylaxis 14 or 42 per cent of the 33 girls of the control group showed no enlargement but so did 9 or 15 per cent of the 8 girls who received iodine.

In 1929, Shore and Andrew (92) stated that there had been no change in the incidence of goiter in New Zealand since 1925, in spite of the use of iodine, but that the goiters encountered were smaller.

Ash (6), in Derby, England, found that the incidence of goiter among school girls increased even though they received 0.1 grain of iodine, as sodium iodide, weekly for eleven months, except for seven weeks of vacation.

It is probable, therefore, that such beneficial results as have been obtained with the prophylactic use of iodides are due, not to their making good a deficiency, but some pharmacodynamic action.

There are a large number of chemical agents that will produce marked enlargement of the thyroid in animals that receive diets that are otherwise quite satisfactory and that contain comparatively large quantities of iodine [see Astwood (7, 8) for a review and for additional references]. Therefore it is possible that a biological agent should produce a similar effect. Since there is no satisfactory evidence for the "iodine-lack" hypothesis and since the history of goiter in many countries is that of a newly introduced epidemic disease (36), which became endemic in some places, with considerable temporal variations in severity, it is believed that endemic goiter is not a deficiency disease but is due to a biological agent of unknown nature.

VII. SUMMARY

The "iodine-lack" hypothesis has been submitted to critical examination with the following results:

1. The evidence that there is a deficiency in the iodine intake in goitrous regions is faulty in that the proponents of this view have not properly controlled their analytical techniques nor their collection of food, water and excreta. It has been found that different varieties of the same vegetables, grown upon the same soil and at the same time, show a greater variation in

their iodine contents than the differences claimed to exist between foods produced in goitrous and non-goitrous areas. Moreover, many of the reports available, particularly those of investigations in which the analytical work has been best controlled, do not show the postulated differences in iodine supply.

2. A negative correlation between the weights of the thyroids and their iodine contents could not be demonstrated in any one of 23 series of analyses by 17 different observers. Such correlation as has been found to exist is **positive,** the **larger** glands tending to contain the **larger** amounts of iodine. The correlation coefficients varied from 0.02 to 0.88.

3. Persons with goiter do not show the usual sign of thyroid insufficiency; viz.: a low metabolic rate.

4. Goiters have been produced in rats upon certain iodine-poor diets, but the addition of such small quantities of iodine as are found in ordinary diets has not prevented, nor lessened, the enlargement of the thyroids. Glands of normal size and microscopical appearance have been obtained in rats upon such diets, only by the use of much larger amounts of iodine and the accumulation of abnormally high concentrations and amounts in the thyroids.

5. The prophylactic administration of iodine to humans has not reduced the incidence of new goiters to zero. In fact, in some cases there has been no effect at all, or even an increase in the incidence. The beneficial effects, such as they were, appear to have been due, not to the making good of a deficiency, but to a pharmacodynamic action of iodides. Some of the apparent effects appear to have been produced by changes in the virulence in the disease, brought about by factors of unknown nature.

It is concluded that endemic goiter is not due to a lack of iodine.

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THE EFFECT OF ORAL THYROID MEDICATION UPON THE PROTHROMBIN TIME

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PRIOR to the free use of iodine in the treatment of Graves' disease a significant number of cases developed cirrhosis of the liver (2). The belief that hepatic dysfunction was in a great measure responsible for post-operative thyroid crises prevalent in the pre-iodine periods is strengthened by the striking similarity between these reactions and those frequently observed in cholemia after traumatic or surgical shock. Graves' disease is of complex activity. The question posed is whether thyroid excess exerts adverse effects upon the liver. The literature on the subject is very meager and evidently its implications have been little appreciated. The relationship becomes clinically significant because of the enormous and ever increasing quantities of thyroid extract used for therapeutic purposes.

A study was made to learn whether altered liver function could be demonstrated in a group of patients given thyroid medication in substantial doses over varying periods of time.

HEPATIC FUNCTION TEST

Prolongation of the diluted (12.5%) plasma prothrombin time is at least one of the earliest detectable functional changes demonstrable in liver disease. It occurs in hepatic disease induced experimentally in dogs by carbon tetrachloride as well as that occurring clinically in man (3, 4, 9). It is detectable earlier in the disease than abnormalities in other function tests including bromsulfalein retention.

The liver is the site of prothrombin elaboration, and prothrombinopenia unless proved to be of another origin, is viewed as a reflection of the state of this function in the liver. If the prothrombinopenia fails to disappear following adequate doses of Vitamin K, the assumption is that there is hepatic functional pathology.

This procedure was used in the present study to detect disturbed liver function in the patients receiving thyroid therapy.

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METHOD OF PROTHROMBIN ASSAY

The procedure used is that described in earlier communications (5, 6). It includes estimation of the prothrombin time of both whole and diluted (12.5%) plasma. The test requires a thromboplastic agent of high standardized potency. In our hands a preparation of desiccated fresh rabbit lung has proved most satisfactory.[1] The technic utilizes a precise and unmistakable end-point in which the clot is lifted the instant it forms, from the otherwise clear fluid.

The normal standards are as follows: Whole plasma prothrombin time, 14–17 seconds; diluted (12.5%) plasma, 37–42 seconds. All estimations are made in duplicate after incubation of the plasma at body temperature for fifteen minutes.

MATERIAL AND PROCEDURE

Sixteen subjects constitute the present series. Eleven were females. The ages varied between 18 and 56 years. Seven were cases of obesity, two were cases of chronic undernutrition in which high caloric diets plus vitamin concentrates had failed to effect improvement in weight, and in which the thyroid medication was administered to stimulate metabolic interchange. Two were cases of thyroid deficiency, one post-operative and one spontaneous, and two were cases of "burned-out" rheumatoid arthritis. The series also included two cases of cardiac disease exhibiting good circulatory control after maintenance doses of digitalis. One of the group was a case showing symptoms of the menopause, and in which the basal metabolic rate was −19 per cent. One of the cases of obesity desired to reduce weight speedily, and was given one gram (15 grains) of the thyroid preparation daily for ten days.

The initial prothrombin time was normal in all but two cases. These two presented evidences of chronic undernutrition. During the period of study the diet in each case was adequate in protein content and accessory factors. No vitamin K was administered but the use of leafy vegetables was permitted according to the desires of the respective individuals. Two of the cases had had subtotal thyroidectomy for Graves' disease more than two years previously. One (*Case #15*) had chronic auricular fibrillation and received maintenance doses of digitalis during the study. There was no failure of the circulation in any of the cases.

THYROID MEDICATION

The preparation used was a highly purified thyro-globulin, termed *Proloid*, which contained 0.2% organic iodine, the U.S.P. level. It was

[1] The thromboplastin used in this study was supplied by Dr. Ralph Overman of The Maltine Company, Brooklyn, New York.

administered orally and was used in preference to ordinary desiccated thyroid to obviate the possibility of other substances being present in the desiccated gland substance which might exert an influence upon prothrombin. In none of the cases was any evidence of toxicity noted despite the relatively large doses used, with the exception of *Case #15*, in which an unusual acceleration of the ventricular rate occurred toward the end of the experiment. This patient had auricular fibrillation and required additional digitalis to control the tachycardia despite the withdrawal of the hormone. On the other hand the obese patient in whom rapid weight loss had occurred after daily doses of one gram for ten days, showed no acceleration of the heart rate despite an increase in the basal metabolic rate from +12 per cent to +40 per cent and a loss in weight from 87.2 kg. (192 lb.). to 83.2 kg. (183 lb.). This has been observed by other workers (8). With the exception of the latter case, the dosages administered to the other subjects varied between 0.1 gm. (1½ grains) and 0.3 gm. (5 grains) per day. Eight cases received the medication for four to five weeks. One case was given 0.15 gm. (2½ grains) daily for 104 days. The remainder of the cases were treated for periods varying between two and three weeks.

ANALYSIS OF RESULTS

Fourteen cases exhibited normal initial prothrombin time of both the whole and diluted (12.5%) plasma. In all of these the prothrombin time remained normal at the termination of the respective periods of thyroid medication. Of the two cases which yielded prolonged prothrombin time at the outset, one returned to normal and the other remained prolonged. In this latter instance Vitamin K administration failed to produce reduction to normal. The interpretation is that hepatic insufficiency was present. It is noteworthy that the patient gained about 2 kilos in weight during the period of study, despite the apparent failure of the liver function to improve.

COMMENT

The data herein presented indicates that the administration of thyroid for therapeutic purposes continued over periods averaging about a month, is attended by no alteration in prothrombin time of the diluted (12.5%) plasma. In view of the highly sensitive indicator of hepatic function which this test has been demonstrated to be, it seems reasonable to conclude that the medication described is without ill effect upon the liver, at least in respect to the function of prothrombin formation. It is worthy of emphasis that in every instance the food intake was adequate from the standpoint of protein content and accessory foods. The results might be otherwise in cases receiving insufficient quantities of essential food components. The two cases of undernutrition suggest that this may be so. The fact that one of these yielded values indicative of restoration to normal suggests that

Case No.	Initials	Sex	Age	Diagnosis	Daily dose gm.	Duration of medication days	Basal metabolic rate		Prothrombin time				Remarks
									Before Rx.		After Rx.		
							Before Rx.	After Rx.	Whole plasma	Diluted plasma	Whole plasma	Diluted plasma	
1.	*I.S.*	M	26	Obesity	0.3	21	+12%	+22%	16	39.8	17.2	41.6	Rheumatic heart disease; not in failure.
2.	*M.B.*	F	24	Obesity	0.15	27	−11%	+14%	15.6	38.8	16.4	39.0	Post-thyroidectomy
3.	*B.L.*	F	39	Early menopause	0.3	22	−19%	+ 3%	15.4	37.0	17.7	38.0	Estrogenic hormone also given during study.
4.	*F.S.*	F	25	Obesity	0.3	20	+13%	+17%	16.2	37.0	16.6	39.4	Received hormone therapy for oligomenorrhea and sterility.
5.	*B.E.*	F	56	Hypothyroidism	0.15	104	−19%	+ 6%	14.8	38.0	16.0	40.2	Spontaneous thyroid deficiency.
6.	*T.F.*	M	18	Obesity	0.3	30	+14%	+16%	16.5	39.5	17.0	39.8	
7.	*B.F.*	M	48	Obesity	0.3	26	+ 9%	+14%	17.0	38.6	16.8	40.2	
8.	*R.K.*	F	29	Undernutrition	0.1	14	− 2%	+ 3%	19	51.0	19.5	56.0	Etiology of under nutrition obscure. Wt. 40 kg. (88 lb.) at outset. Gained (4.5 lb.) 2 kg. during study.
9.	*I.O.*	M	46	Undernutrition	0.15	20	− 4%	± 0	20	54.6	17.0	41.2	Prolonged nervous strain for years; no weight gain during study.
10.	*A.W.*	F	45	Obesity and menopause	0.3	30	−10%	+ 1%	16	39.5	16.5	40	Estrogenic hormone also administered during study.
11.	*E.S.*	F	30	Rheumatoid arthritis	0.15	36	−13%	− 4%	14.6	38.5	14.2	39.2	
12.	*T.D.*	F	33	Rheumatoid arthritis	0.15	36	−14%	− 3%	14.0	36.0	14.8	38.0	
13.	*F.B.*	F	45	Cardiac disorder	0.15	36	− 9%	+ 1%	13.3	36.8	14.2	39.0	Receiving maintenance dose of digitalis; free of failure during study.
14.	*B.C.*	F	45	Cardiac disorder	0.15	36	− 9%	+ 5%	14.2	39.8	14.8	41.0	Receiving maintenance dose of digitalis—(not in failure).
15.	*F.Q.*	F	39	Hypothyroidism	0.15	30	−17%	+ 5%	14.8	38.0	15.0	40.2	Post-thyroidectomy; digitalis therapy; auricular fibrillation.
16.	*M.B.*	M	45	Obesity	1.0	10	+12%	+40%	16.0	39.5	16.5	41.0	

stimulation of metabolic processes induced by the thyroid substance might have augmented the synthesis of prothrombin. In this case the liver must have been adequate. In contrast, the other patient who failed to show improvement in prothrombin elaborating function despite a weight gain may have been suffering from an antecedent hepatic deficiency which con-

tinued unaltered after thyroid medication. The behavior of cases of Graves' disease in the active stages when colonic hyperactivity is prominent suggests the background for hepatic disturbance as noted by earlier investigations. Diminished absorption and accelerated excretion of foodstuffs give rise to a state of chronic undernutrition akin to that seen in long standing colitis. An added factor is the augmented metabolic rate which increases the consumption of essential substances. The net result is similar to prolonged undernutrition, especially of proteins, which predispose to hepatic degeneration (1). The observation of Williams and co-workers (7) that the blood level of thiamine in the presence of "thyrotoxicosis" is below normal is significant in this respect.

It is suggested that the hepatic disturbance found in Graves' disease results from chronic undernutrition rather than from any direct action of excess thyroid hormone on the liver. This state of undernutrition is due to increased demand for essential substances as a result of the high metabolic rate, to diminished intestinal absorption and to accelerated excretion.

SUMMARY

Doses of from 0.1 gm. to 1 gm. (1½ to 15 grains) of thyroid globulin (*Proloid*) were administered daily to sixteen patients for from ten to 104 days. None showed an increase in the plasma prothrombin time.

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EXTREME INSULIN RESISTANCE: A CASE STUDY[1]

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DESPITE a wealth of experimental and clinical data, many problems concerning the nature, course and control of carbohydrate metabolism under both normal and abnormal conditions still demand elucidation. The more some of these are investigated, the more numerous become our points of view. Thus it is with the phenomenon of insulin resistance, which more and more appears to be a syndrome that follows any of a number of precipitating factors, rather than a sharply defined clinical entity capable of unified consideration and management. Inasmuch as less than 50 cases of "true" insulin resistance have been reported to date (9), the following patient, in whom severe pancreatic and hepatic dysfunctions have been proven to exist, offers further historical and laboratory data which may throw light upon some of the difficult problems concerned with extreme resistance to insulin.

CASE REPORTS

A.L., a 65 year old Hungarian-born fruitman and former wrestler, was transferred from the City Hospital to the Metropolitan Hospital on November 11, 1945, because of polyuria and polydipsia, and a history of two episodes of "insulin resistance," one in 1939 and the other in May, 1945.

Since the age of 23 he has been subject to asthmatic attacks, which have been very mild in the past several years. Between the ages of 30 and 40 he drank 10 or more beers daily and some whiskey. He has used very little of this in the last 10 years. At the age of 40, he was confined to bed for six weeks for an "enlarged and hard liver" without jaundice; a surgical procedure was suggested at this time and refused. In 1941, a nephrectomy was performed for a hypernephroma. He sleeps well, uses coffee moderately, smokes 10 to 12 cigars daily, and suffers from constipation of moderate degree.

The present troubles began in July, 1939, when he complained of nocturia, polyuria, polydipsia, blurring of vision and dizziness. A diagnosis of diabetes mellitus was established. In November, 1939, he was admitted to the City Hospital after a well kept dietary regime and 70 units of protamine zinc insulin daily failed to bring about any control. His history and course at that time have already been described in detail by one

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of us (13). In the first four days of that hospitalization he required 2310 units of insulin with a maximum of 910 units administered on the third day. From the fifth day, acidosis began to recede, and by the end of seven weeks he was aglycosuric and normoglycemic without insulin therapy, Indeed, as little as 10 units of insulin then produced shock. Following the first dose of insulin and for the next four days, generalized and localized allergic reactions required the repeated use of adrenalin. Neither the liver nor the spleen were palpable at this time.

He was asymptomatic from the time of this first episode until May, 1945, when he returned to the clinic with a recurrence of his former symptoms. A controlled diet and 125 units of protamine zinc insulin daily failed to relieve him. Therefore, he was read-

TABLE 1. BLOOD CHEMICAL FINDINGS (*A.L.*)

Date	Day	I.I. (units)	Phosphatase (units)	CO_2 C.P. (Vol. %)	Proteins		Mg. per 100 cc.					Remarks
					Total (%)	A/G	Cholesterol		N.P.N.	Urea N	Creatinine	
							Total	Free				
11/14/45	1	5.1	4.8		7.8	2.0	166	55		12.5	1.1	Glycosuria and ketonuria
11/19/45	6			58						15.0	1.3	
12/30/45	45									17.5	1.5	
1/14/46	61									13.0	1.7	
2/25/46	103								40.0	18.5	1.7	
3/ 4/46	110	5.0	4.0		7.5	2.7	170	50	48.0	23.5	2.1	
3/11/46	117	5.2	4.0		6.9	2.6	140	40	49.0	22.5	2.2	
3/18/46	124	5.2	5.0		6.2	2.6	150	50				
3/25/46	131	5.6	5.2		7.8	1.6	170	50	32.0	15.0	1.3	Sl. dehydration;
4/ 1/46	138	5.1	4.0		8.0	3.0	160	50	40.0	17.5	1.6	acute pancreatitis.
4/ 8/46	145	5.0	5.0		6.9	2.45	130	40		13.5	1.2	Dehydration gone; convalescing
4/15/46	152	5.1	3.1		6.6	2.3	120	40		15.0	1.3	
4/22/46	159	5.1	4.8		5.7	2.3	120	40				Controlled
5/ 6/46	174	5.2	3.8		5.6	2.0	126	40	52.0	13.5	1.4	
5/13/46	181								40.0	16.0	1.4	

mitted to the City Hospital on September 24, 1945. He had lost 12 pounds weight in two weeks. He had ketonuria, 4 plus; glycosuria, 4 plus; and a blood sugar value of 250 mg. per 100 cc. His physical examination on admission revealed an obvious loss of weight and a liver edge palpable 2½ fingers below the costal margin. His spleen was not detectably enlarged.

He was given a measured diet containing C. 150, P. 75 gm. and F. 75 gm., amounting to 1575 calories. Doses of 300 units of unmodified insulin[2] were given subcutaneously at eight-hour intervals for 12 doses without materially influencing his ketonuria, glycosuria or hyperglycemia. Following an additional 300 units of unmodified insulin intravenously he developed shock. For two days his urine remained sugar free while he received a single dose of 90 units of protamine zinc insulin daily and the above diet. Glycosuria then returned in as marked a degree as before but without ketonuria. Two hundred units of

[2] The term "unmodified" is used here and subsequently to designate unaltered insulin or insulin as originally purified. While certain objections may be raised to such usage, it certainly seems preferable to the commonly employed adjective "regular," which implies that here is something "irregular" or abnormal about all other preparations of the hormone.

protamine zinc insulin daily for five weeks failed to alter this. However, his general clinical condition was good, and at no time during this or his previous hospital stay in 1939 and 1940 had he shown any clinical evidence of coma or of severe disturbance of the acid-base balance.

Insulin was discontinued, because of repeated local and systemic allergic reactions and because his clinical condition seemed satisfactory despite severe glycosuria and hyperglycemia. Eight days later he was admitted to the Metropolitan Hospital. His fasting blood sugar was 310 mg. per 100 cc.; there was a 4 plus glycosuria, a 4 plus acetonuria and a 2 plus diaceturia.

TABLE 2. RESPIRATORY QUOTIENT IN RELATION TO OTHER FACTORS

Date	Day	Insulin daily units*	Fasting blood sugar	Urinary			R.Q.		
				Sugar	Acetone	Diacet. acid	Fasting	Bkft.	Lunch
								1 hr. after	
11/14/45	1	0	310	++++	++++	++			
1/ 4/46	51	200**	610	++++	++++	+	0.82	0.71	0.77
1/14/46	61	200	500	++	0	0	0.88	0.92	0.96
2/ 7/46	85	200	420	++++	0	0	0.93	0.80	0.94
3/ 6/46	112	400		++++	++	0	0.88	0.81	0.77
3/25/46	131	350	325	++	++	0	0.80	0.84	0.88
3/26/46	132	250		+++	F.T.	0			
3/27/46	133	175		+	+	0			
4/ 1/46	138	175	91	−	0	0	0.81	0.90	0.91
5/ 1/46	168	30	84	+	0	0			
		(12)		−					
5/14/46	181	15	126	+	0	0			
		(6)		−					

* Began on date noted.

** Actually began 1/5/46.

The physical examination revealed an individual who showed an obvious loss of weight (wt. 60.8 kg., 134 lb.). His pulse was 72 per minute, and his blood pressure 130/75 mm of mercury. The skin was pale and dry. There was some tortuosity of the fundal blood vessels, and thickening of the walls of periphreal vessels. His liver presented a hard, non-tender surface with the lower edge extending two and one-half fingers below the right costal margin. A firm, freely movable spleen was readily palpable at a level two fingers below the left rib border. No other noteworthy physical signs were present.

On admission his hemoglobin was 17.0 gm. (100 per cent); the hematocrit, 47 per cent; the erythrocyte count, 4.65 million per cu. mm.; the leucocyte count, 15,400 per cu. mm.; the differential count (expressed in per cent) polymorphonuclear neutrophiles, 57; eosinophiles, 2; basophiles, 0; lymphocytes, 41; and monocytes, 0. The carbon dioxide combining power of the serum was 58 volumes per cent; the icteric index, 5.1; the van den Bergh and cephalin flocculation reactions, negative; the alkaline phosphatase of the blood. 4.8 Bodansky units; and the prothrombin determination, 100 per cent. The values

for the serum proteins (per cent) were: total. 7.8; albumin fraction, 5.2; and globulin fraction, 2.6; the A/G ratio was 2.0. Other chemical constituents of the blood, in milligrams per 100 cc., were: total cholesterol, 166; cholesterol esters, 111; urea nitrogen, 12.5; creatinine, 1.1; also in milliequivalents per liter, sodium, 141.7; potassium, 5.0; and chloride 103.7.

With the exception of the estimations for electrolytes, these blood chemical determinations were repeated frequently throughout the entire period of observation. Variations were significant in the following regard. The initial total cholesterol of 166 mg. per 100 cc. fell to 120 mg. per 100 cc. when the patient was finally controlled; there was no change in the free-total ratio. Except during the acute abdominal episode, when the figure was 4 per cent, the value for total serum protein rose and fell with the state of hydration and was 5.6 per cent when determined on the 181st day of hospitalization (Table 1). The

TABLE 3. REACTIONS WITH BLOOD SERUM OF *A.L.*

Clinical Condition	Insulin		Patients' blood		Remarks
	Dose (units)	Period (wk.)	Reagins	"Anti-insulin substance"	
Uncontrolled	0	−8*	++++	0	
Glycosuria	200	5	++++	0	Urticaria
Uncontrolled		8	—	0	Urticaria gone
Uncontrolled	400	3	++++	—	Pancreatitis
Controlled	15 (6)	3	++	0	

* Minus signs denotes time "off insulin" just prior to making this series of tests.

albumin-globulin ratio was above 2.0 except for the period of the acute abdominal upset when a value of 1.60 was obtained (Table 1.)

In addition to the glycosuria and ketonuria already mentioned, a complete urinalysis revealed a specific gravity of 1.032; a pH of 5.0; a two plus albumin; an occasional erythrocyte, a few leucocytes; a few granular casts; and a moderate number of epithelial cells.

The patient was given a diet of C. 125 gm., P. 70 gm., and F. 70 gm., with calories amounting to 1410. He was also given a general vitamin supplement of two to three times the minimum daily requirement established by the Food and Nutrition Board National Research Council. For approximately eight weeks no insulin was given. At the end of that time the fasting blood sugar was 610 mg. per 100 cc. Glycosuria and ketonuria were both 4 plus (Table 2) although ketonuria had been absent a portion of the intervening time. His weight was unchanged, and while he complained of weakness and had shown a polyuria (2600 to 3400 cc. of urine daily), the general clinical condition did not suggest that commonly seen in long lasting acidosis.

On January 5, 1945 (51st hospital day), injections of unmodified insulin, 100—50—50 daily, were started. To this the patient showed a satisfactory response during the first eight days; there was a complete disappearance of acetonuria and a reduction of glycosuria to a negligible amount. However, severe local reactions and widespread urticaria occurred. Moreover on the ninth day of insulin administration there was a mild shock.

Because of this the noon-day dose of insulin was omitted for two weeks with a gradual reappearance of 4 plus glycosuria and 0 to 2 plus acetonuria . There was no change when the injection of 200 units of insulin daily (Table 2) was resumed. The allergic responses to insulin disappeared in about seven weeks, despite its continued use. However, reagins were demonstrable in the patient's blood at all times (Table 3). On March 6, 1945, because of continued resistance to insulin the dose was raised to 200—100—100 units. Three weeks later it was necessary to reduce the dose to avoid shock (Table 2). Tolerance has continuously improved since that time. At present (June 15, 1946) the patient is normoglycemic, aglycosuric, without ketonuria, while taking a mixture of seven units of unmodified and three units of protamine zinc insulin given as a single dose every morning.

TABLE 4. LABORATORY DATA (*A.L.*)

Date	Day	Blood Count			Differential Leucocyte Count (%)						Serum		Remarks
		Hb. (gm. 100).	R.B.C. (cu. mm.)	W.B.C. (cu. mm.)	Polys		Lymph.	Mono.	E.	Bas.	Amylase (Wohl. U.)	Lipase (cc./0.1 NaOH)	
					Mat.	Im.							
11/14/45	1	17	5.65	15,400	57		41	0	0	2			In acidosis
12/27/45	43	16	4.44	9,200	58		42	0	0	0			Acidosis improved
1/ 4/46	51	15	4.51	6,550									Insulin started
3/27/46	134										32	0.9	
4/ 1/46	138	14	4.04	32,000	58	23	18	1	0	0	32	1.1	Acidosis±
4/ 4/46	141			18,950	62	16	21	1	0	0			
4/ 5/46	142			14,100	61	17	18	4	0	0			
4/ 9/46	146	16	4.45	36,900	41	16	41		2		16	1.3	
4/23/46	160	14	4.52	20,200	70		30	0	0	0			
4/30/46	167	15	4.83	18,250	78		20	2					Diabetes controlled
5/15/46	182	14	4.79	9,700	56		40	1		3			

On March 19, 1946, the 125th hospital day, (Table 2) the patient developed a slight fever and had nausea and vomiting, and complained of left subcostal pain radiating forward from the spine. Simultaneously his liver enlarged until the edge was palpable five fingers below the right costal margin, and his spleen became more readily felt. The height of this attack was reached eight days later, at which time a mass the size of a grapefruit was palpable to the left of and above the umbilicus. This was tender, rounded smooth, soft in consistency, only slightly movable and lay behind the stomach or the stomach and transverse colon. The patient showed appreciable improvement by April 3, 1946. At the present time no mass is palpable and the liver has receded to its former size. Changes in the blood count during this acute episode are recorded in Table 4. Repeated determinations of serum amylase and lipase were consistently normal throughout this acute illness, varying from 16 to 32 Wohlgemuth units and from 0.9 to 1.3 degrees respectively (Table 4).

Changes in the respiratory quotient throughout the patient's hospitalization are recorded in Table 2 and the results of special tests for specific substances in the blood stream associated with insulin resistance are noted in Table 3.

The diagnostic impressions were: diabetes mellitus; insulin resistance; status allergicus; acute pancreatitis, with retention cyst or pseudocyst of the pancreas; chronic pancreatitis with fibrosis and atrophy; hypertrophic cirrhosis of the liver; and moderate generalized arteriosclerosis.

METHODS AND RESULTS OF SPECIAL TESTS

Tests made for reagins to insulin in the blood of the patient according to the Prausnitz-Kustner technic as described by Tuft (38) were routinely positive, even when 0.02 cc. of a 1:20 dilution of the patient's serum was employed (Table 3). The degree of reaction as determined by the dilution of the patient's serum varied moderately from time to time but was always strongly positive. This was true in periods without insulin, and with insulin when the patient was uncontrolled, as well as when fully controlled. The reaction was weakest under the last-mentioned conditions (Table 3).

Tests were made for the presence in the blood of the patient of "anti-insulin substances" or "insulin neutralizing substances" according to the method of Lowell (24), slightly modified as to number of animals and serum dilutions. However, in no instance were less than five mice used in any single determination, nor was the amount of serum ever less than that mentioned by him. As high as 0.5 cc. of serum were given per mouse. By this method we were unable to demonstrate any material in the blood of the patient capable of protecting a mouse from a convulsive and usually fatal dose of insulin (0.033 unit) (Table 3).

DISCUSSION

In 1929, Root (30) laid down very satisfactory criteria for the definition of insulin resistance, by which Martin *et al.* (26) have recently examined critically 26 cases reported in the literature and added one of their own. Since then Felder (9) has collected others and added one of his own. Among the recent cases not reviewed by him should be included those of Brentano (4), Jordan [two cases (16)], Lawrence (18), Levi and Freedman (20), Lozinski and Frohlich (25), Pullen and Sodeman (29), Schloss (33), Shepardson *et al.* (34), and Werner (42).

In the present patient, the condition of insulin resistance existed for more than 48 hours, and on several occasions required a great deal more than 200 units of insulin for control. It, therefore, belongs in the insulin resistant group described by the above authors. Emphasis upon several points seems relevant:

1. **There were three severe episodes of insulin resistance, after each of which the diabetes has been so mild as often not to require any special insulin or dietary regime.** Three attacks in at least one other patient have been observed (39). Patients requiring no insulin prior to their attacks have been described (5, 7, 8, 35), and the majority of patients developing such episodes have been found among those with a mild form of the disease.

2. **Reagins for insulin were found in the blood stream.** Severe local and generalized urticarial reactions to insulin have been regarded as the precipitating factor in at least three patients with insulin resistance (2, 10, 31),

and in five others similar allergic reactions are known to have occurred in relation to the use of insulin (17, 23, 24, 27, 34). Passive transfer of sensitivity has been attempted in 11 patients (1, 5, 9, 17, 21, 22, 23, 24, 25, 27, 35, 41). The test was positive in three (17, 21, 23, 24). Lowell has called attention to the fact that such reagins may be present in the blood when the patient is showing no clinically detectable allergy or resistance to the action of insulin. This has certainly proven true in the case herewith reported, although the titre of reagins was definitely highest at the height of his resistance when as little as 0.02 cc. of a 1:20 dilution of his serum produced a severe reaction in the passively sensitized individual. Inasmuch as the urticarial reactions disappeared in our patient while he was still requiring daily doses of insulin in excess of 200 units, it seems unlikely that such reactions were a very important factor, if a factor at all, in the production of his clinical condition.

The question of allergic antibodies to insulin within the blood stream raises a most important therapeutic question. Is it possible to produce severe generalized reactions, even associated with anaphylaxis and death? In a study of the protocols of the fatal cases of Almy *et al.* (3) it is suggestive from the type of liver damage that these patients died of anaphylactic shock. Other authors have mentioned the fact that their patients must have died from the effect of insulin itself. Preliminary studies with our patient lead to the suggestion that epinephrine and drugs of the type of benadryl may be successful in preventing serious complications or fatality as a result of allergic or hyperergic sensitivity to insulin.

In contrast with this viewpoint is that of Lerman (19), who believes that the best cure for overcoming insulin resistance is its repeated administration, rather than its omission. Clinically, it is quite clear that the **allergic reactions decrease rather than increase** with succeeding doses. Nevertheless, all "resistance" is certainly not on an allergic basis.

3. **"Insulin neutralizing substances" were not found in the blood stream.** Lowell (23, 24), Felder (9), Wayburn and Beckh (40), and Glen (11) have observed that the blood serum of their insulin resistant patients was capable of protecting small laboratory animals from convulsive or fatal doses of insulin. No further identification of the nature of the protective agent has been attempted, although Lowell refers to it as a "neutralizing antibody." Its actual point of attack upon the action of insulin is equally undetermined. Such a substance or substances were not found in our patient, nor were they detected in seven other patients in whom search was made (1, 5, 10, 17, 25, 35, 41). Presumptively, such substances tend to inhibit the activation of hexokinase by insulin. Felder (9) emphasizes the fact that there is no lack of insulin kinase, as was originally postulated by Himsworth (15). Of 25 diabetic patients tested, Rushton (32)

found six whose blood plasma decreased the hypoglycemic effect of insulin upon the blood sugar of rabbits. However, they found it impossible to correlate such activity "with any other peculiarity of the patients or to use this effect of the blood plasma to identify a separate type of diabetes."

4. **Rather prolonged periods of ketosis occurred without clinical evidence of coma.** For the first three and one-half weeks of his third episode of insulin resistance our patient showed acetone bodies in the urine continuously, but at no time presented the picture commonly seen as a result of such ketosis. Clay and Lawrence (8) reported the death of such a patient, and then state that he was not in coma at any stage of his illness. It seems, therefore, that the majority of these insulin resistant diabetics stand ketosis well. Neither this fact nor the mildness of the diabetes between attacks seems as yet to have been satisfactorily explained by our knowledge of the alterations of intermediary carbohydrate metabolism in diabetes.

5. **Infection and inflammation did not play a leading role.** Much has been written on this subject, and the increased requirements for insulin in the presence of any such process are too well known to need elaboration. In the present instance, nevertheless, it does not appear that the inflammatory or infectious element of the acute abdominal episode played a leading role in the resistance to insulin for when this was at its height, the patient's tolerance for carbohydrate was already improving, and his insulin requirement decreasing. Moreover, although infection is a commonly accepted cause of insulin resistance, it never produces such an extreme state.

Almost any type of toxemic process may cause hepatic damage. Taubenhaus and Soskin (37) have suggested that toxemias may cause insulin resistance by inhibiting phosphorylating mechanisms, while allowing blood amylase to enter and break down glycogen. Since insulin does not influence this abnormal pathway for glycogenolysis, according to them, an abnormally small response to insulin results.

6. **Disease of the pituitary, thyroid, and adrenal glands was not found.** We were completely unable to establish the presence of any abnormality or active disease process in the pituitary, thyroid, or adrenal to account for the lack of responsiveness to insulin in our patient. However, from the case reported by Hart and Greene (12), in which a quiescent acromegaly was associated with insulin resistance, it is apparent that an already hormonally inactive condition of an endocrine organ may be associated with or lead to insulin resistance.

7. **Generalized arteriosclerosis was moderate.** Held (14) has suggested that sclerosis of the arteries of the pancreas produces a syndrome in which upper abdominal pain; a mild diabetic state, refractory to, but requiring little insulin; and hypertension are the major features. Generalized

sclerosis was moderate in our patient and hyperpiesis absent. However, his condition did resemble that mentioned by Held (14), to the extent that the acute pancreatic episode was not associated with a rise in serum amylase or lipase.

8. **Disease of the liver and pancreas was present.** When all factors in the history and physical examination are taken into account, it is difficult to escape the conclusion that our patient suffered from a cirrhosis of the liver, and from a diffuse fibrosis and atrophy of the pancreas, superimposed upon which was an acute pancreatitis and the development of a retention cyst or pseudocyst. Newburgh (28) and Taub and his associates (36) have emphasized the importance of hepatic disease in the production of an insulin insensitive type of hyperglycemia. Into this category they believe the majority of so-called older "diabetics" should fall. They stress the facts that such patients tolerate hyperglycemia well, for long periods of time, and may have bouts of ketonuria without the clinical picture of coma. Moreover, they feel that it makes little difference in the clinical picture whether or not they receive small or large doses of insulin, as they are relatively insulin insensitive. They postulate a primary hepatic disturbance in such individuals, which interferes with one or more of the enzyme systems concerned with intermediary carbohydrate metabolism within the liver itself.

In reporting a patient who required as much as 2000 units of insulin daily, Lawrence (18) has suggested that the insulin itself interferes with normal hepatic metabolism. In his case, he believed the associated lipoatrophy, hyperglycemia and lipemia were brought about by some factor interfering with the important action of insulin in changing sugar into stored fat. However, he looked upon the disturbance in fat metabolism as primary, and the changes in the liver as purely secondary.

From a clinical viewpoint, it certainly appears likely that the conditions found in our patient have been the result of hepatic and pancreatic disease, in which disturbances of the islands of Langerhans may be more of an incident than a fundamental underlying cause.

On the other hand, we may equally well proceed from pancreatic to hepatic dysfunction. Experimentally, Chaikoff, Connor and Biskind (6) have shown that completely depancreatized dogs, kept under good diabetic control, develop progressive disease of the liver, in which phases predominated by fatty infiltration slowly give way to a picture, clinically and pathologically indistinguishable from cirrhosis of the liver. Our patient's problems may have begun with pancreatic damage. It seems probable that widespread atrophy and fibrosis now exist in that organ, and interfere not only with its endocrine but with its exocrine secretions as well. Secondarily, a relatively mild insulin insensitive type of diabetes mellitus has occurred, which has as its primary feature an intrahepatic interference with the utilization of carbohydrate.

SUMMARY AND CONCLUSIONS

A patient with mild diabetes has been presented who has had three distinct episodes of extreme insulin resistance. Each of these attacks was associated with local and general allergic reactions to insulin. During the third and last refractory period reagins were found in the blood. There was no evidence of any antibodies in the circulation having a direct anti-insulin effect. The fact that the patient had a cirrhotic liver during the entire period and a retention cyst of the pancreas in the last attack, points to a possible hepato pancreatic abnormality as an additional factor in producing and maintaining the insulin resistant state.

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MYXEDEMATOUS DROPSY

Report on a Case of Myxedema with Congestive Heart Failure and Serous Effusions with a High Protein Content

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IN 1925 one of us reported on a number of cases of dropsy appearing in myxedematous patients, characterized by pitting edema of the extremities and pleural and peritoneal effusions (28). The dropsy cleared up on therapy with desiccated thyroid. This condition could be caused either by a disturbance of water and electrolyte metabolism or by cardiac insufficiency ("Myxedema heart" of Zondek, 36). In the cases mentioned above, no obvious signs of congestive heart failure were found, and the dropsy was attributed to a disturbance of salt and water metabolism.

Previously, several cases of myxedema with ascites and pitting edema of the lower extremities have been reported (14, 20, 21). These patients were not in congestive heart failure, and the edema disappeared on the administration of desiccated thyroid. Sven Zandren (35) published observations on dropsy in myxedematous patients to which both cardiac insufficiency and a disturbance in electrolyte metabolism appeared to contribute.

The cases published by Eppinger (8) had progressive edema of the face, trunk, and extremities without definite evidence of cardiac or renal insufficiency. In some, slight albuminuria, slight increase of heart size, and muffled heart sounds were present. Therapy with digitalis and diuretics produced little increase in urine output. Some of these cases responded to desiccated thyroid with marked diuresis and disappearance of edema. Autopsies performed on some of these patients failed to explain the edema. Eppinger emphasized the severity of the edema and drew attention to a number of signs such as brittle nails, loss of hair, dry skin, and umbilical hernia, all of which suggest mild hypothyroidism. However, he stated that the evidence was not sufficient to support such a diagnosis. For the following reasons we believe that the syndrome described by Eppinger is not due to hypothyroidism:

1. Myxedema is more common in females than males. In Eppinger's series there were eight males and one female.

2. In spite of the severity of the edema, no serous effusions are recorded. As has been pointed out previously this would be rare in myxedematous dropsy (5).

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3. Eppinger's patients had severe polydypsia, while in myxedema, thirst eventually disappears.

The diuretic action of desiccated thyroid does not occur only in hypothyroidism. A number of investigators (7, 8, 27, 30), amongst them Eppinger himself, have observed this action in conditions not related to thyroid deficiency. According to Eppinger, this drug would act on the water and salt abnormally stored in the interstitial tissues, rather than on the kidney. However, the action of thyroid preparations on the circulation (decreased circulation time, increased blood volume and cardiac output) may influence renal function.

Since the publication of our paper in 1925, a number of reports have dealt with various aspects of this syndrome (1, 3, 5, 9, 10, 11a, 13, 17, 18, 19, 25, 31). Experimental work (15, 32, 34) as well as clinical observations in this field (2, 4, 5, 12, 16a, 16b, 19, 23, 24, 26, 27) emphasize the frequent appearance of pericardial effusion in myxedema. Some of these investigators believe it to be the main factor in the production of the myxedematous heart. Others like Bullrich (3) and ourselves believe the pericardial effusion to be only a contributing factor to the cardiac insufficiency of myxedema.

In 1925 we suggested two other factors, namely, (28) a disturbance in the salt and water metabolism and congestive heart failure of myxedematous origin. The first factor is illustrated by those cases of myxedema with dropsy, reported by us, which do not exhibit congestive heart failure and whose dropsy shows definite improvement on the administration of desiccated thyroid. An autopsy of a case of myxedema with dropsy has been reported (13) in which evidence of cardiac or renal lesions was absent.

The second cause of dropsy in myxedema, namely, cardiac insufficiency, has been demonstrated by Zondek (36), Sven Zandren (35), and Fahr (11a, 11b). Most of the cases with myxedematous cardiac failure also have chronic lesions of the heart and arteries, yet cardiac tonics and diuretics are in general ineffective, while desiccated thyroid improves both cardiac failure and myxedema. This is well illustrated by a case of congenital myxedema in a girl of 13 published by one of us. This patient had signs and symptoms of heart failure which cleared up completely on the administration of desiccated thyroid.

According to the literature and our own observations, the most frequent cause of dropsy in myxedema is cardiac insufficiency. Cases with only electrolyte disturbances are relatively rare. A combination of the two factors is frequent (5, 29).

We should like to present a case of myxedematous dropsy showing signs and symptoms of congestive heart failure, a marked lymphocytosis and a pericardial effusion with a high protein content.

A.R.S., a 57 year old female, entered the hospital in December, 1942, with the chief

complaint of edema of the eyelids and lower extremities, oliguria, dyspnea on effort, orthopnea, and swelling of the abdomen. She also complained of chilliness, dry skin, poor thirst, reduced perspiration, severe constipation, drowsiness, extensive hair-loss, and joint pains.

The edema of the eyelids, weakness, and constipation had appeared 5 years prior to admission to the hospital. At that time the patient had albuminuria, and nephritis was diagnosed. A nephritic regimen failed to produce any improvement in the patient's condition. Four to five months prior to admission, the dyspnea on effort gradually increased, and shortly before admission the patient had a nocturnal attack of precordial oppression and orthopnea.

Past History: The patient has been generally in good health. She had three pregnancies with normal deliveries. In 1933 the monopause set in.

Family history: Father died of an aortic aneurism.

Physical examination: A tall obese female weighing 112 kg., with marked edema of the eyelids and face and a prominent abdomen. The skin was yellowish, pale, dry, rough, and infiltrated. The mucous membranes were pale, the cheeks and gums infiltrated, and the tongue was beefy.

Cardiovascular system:

Blood Pressure: 150/110 mm. Hg.

Pulse Rate: 84 per min. Occasional premature beats were present.

Heart: No apex beat or thrills over cardiac area could be felt. The heart sounds were muffled.

The neck veins were engorged.

Lungs: Clear.

Abdomen: A prominent abdomen, 126 cm. in circumference. Dullness in both flanks and the hypogastrium; other signs of peritoneal effusion were present. Liver, spleen, or other masses could not be felt. The patient refused an abdominal puncture.

Nervous system: Normal.

Laboratory data:

Urinalysis: Albumin 0.028 per cent. A few white cells were present.

Blood Findings: Urea = 0.02 gm.%
Cholesterol%0.239 gm.%
Magnesium = 0.0023 gm.%
Total Protein = 6.79 gm.%
Albumin = 4.75 gm.%
Globulin = 2.04 gm.%
Albumin-Globulin ratio = 2.3
Blood Wassermann: Negative
Blood Counts
R.B.C. count = 4,500,000 per cu. mm.
White Cell count = 9,000 per cu. mm.
Hemoglobin = 85 per cent

B.M.R.: Minus 3

Venous pressure = 22 cc. of water, increasing to 35 cc. of water on compression of the right upper quadrant of the abdomen.

Circulation time: Arm to tongue (calcium gluconate), 24 sec.
Arm to lung (ether), 13 sec.

Pericardial puncture: 180 cc. of a yellowish fluid were obtained.

Albumin = 4.48 gm.%
Rivolta reaction = positive
Chloride = 0.55 gm.%
Lymphocytes = 85 per cent
Polymorphonuclears = 11 per cent
Endothelial cells = 4 per cent

Fluoroscopy: Enlarged cardiac shadow; no heart beats seen. Diagnosis: Pericardial effusion.

E.C.G.: Sinus rhythm with a rate of 75 beats per minute. Left axis deviation. Low *P* waves. P.R.S. interval 0.12 sec. Inverted T_1; low T_2; positive T_3. Absent R in 4F. The pericardial puncture failed to produce any change in the X-ray configuration of the heart, the E.C.G., the venous pressure, and circulation time.

Treatment: The patient was given a daily dose of 0.05 gm. of desiccated thyroid.

Follow up: 15 days after this treatment was started, the patient felt more active and less chilly. Urine output, perspiration, and thirst increased, and edema of the eyelids diminished somewhat. Skin signs of myxedema, ascites, hoarseness of the voice, heart-shadow on fluoroscopy and heart sounds were not changed. Pulse rate was 88 beats per minute; the blood pressure 175/120 mm. Hg. Venous pressure was 17 cm. of water; and the arm-to-tongue circulation time was 18 seconds. B.M.R. = +30 percent.

The E.C.G. showed an increase in voltage of the *P* waves and of T_1 and T_2. T_1 became positive.

The dosage of desiccated thyroid was increased to 0.1 gram daily.

One month: Marked improvement in the signs of myxedema. Slight puffiness of the eyelids and dryness and pallor of the skin persisted. Weight loss, 13 kg. No nocturnal dyspnea. Daily urine output was about 2.1. Slight edema of the ankles persisted. No signs of ascites. There was a 10 cm. reduction in the abdominal diameter.

Apex beat could not be felt. The apical first sound was muffled. Neck veins were engorged. Blood pressure: 160/90 mm. Hg. Circulation times: Arm to tongue = 17 sec. Arm to lung = 7 sec. On fluoroscopy, a slight reduction of the cardiac shadow and visible heart beats were observed. The E.C.G. showed increased voltage of all waves being most pronounced in the P_4 and T_4.

Blood cholesterol: 0.183 gm. per cent.

One and a half months: The patient had been receiving daily 0.1 gm. of desiccated thyroid resulting in a marked improvement of all signs and symptoms of myxedema. Slight edema of the ankles persisted.

Fluoroscopy of the heart revealed a reduction in the cardiac shadow and the beats could be seen.

Blood cholesterol: 0.195 gm. per cent.

B.M.R.: plus 34 per cent.

Nine months: The patient feels much improved; she reports a marked increase in activity, and can do the housekeeping without dyspnea. Signs and symptoms of myxedema have almost all disappeared. Slight edema of the ankles persisted but may be due to varicose veins. The skin does not show any infiltration. Hair loss has stopped, and new hair is appearing. Speech is fluent, and hoarseness has disappeared. The precordial oppression and dyspnea on effort have not reappeared. Some constipation persists. Muffled apical first sound. Pulse rate: 76 beats per minute and regular. Blood pressure: 195/100 mm. Hg. Venous pressure: 15 cm. of H_2O. Circulation time: Arm to tongue = 18

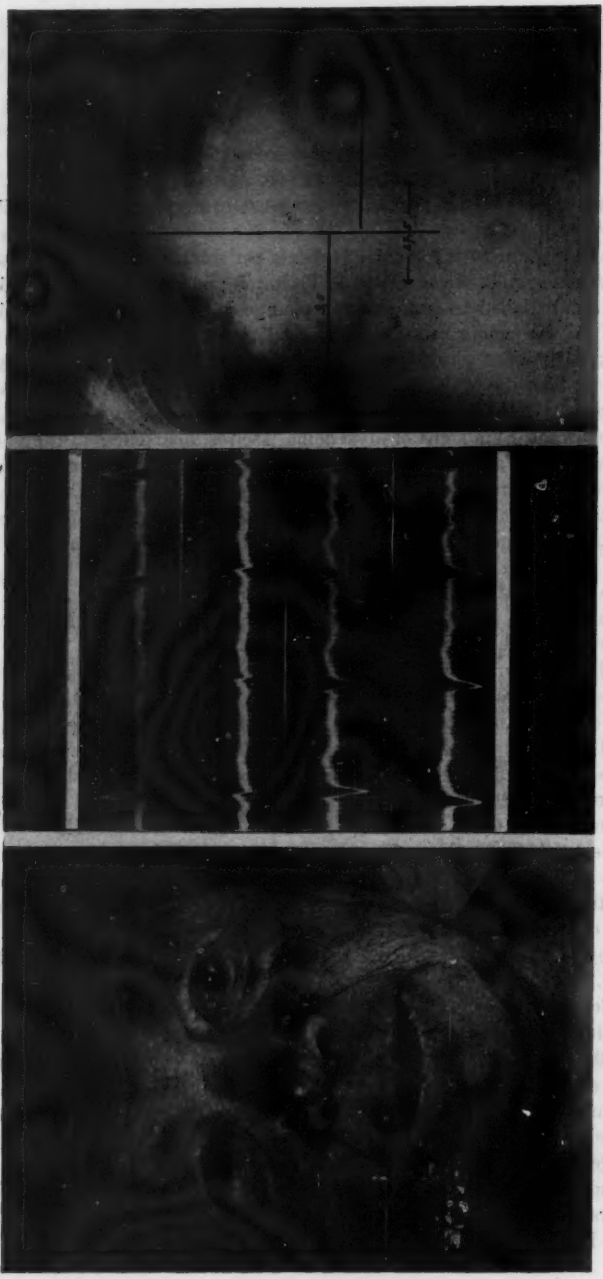

FIG. 1. Picture, electrocardiogram, and teleradiography of the patient before the treatment with thyroid extract.

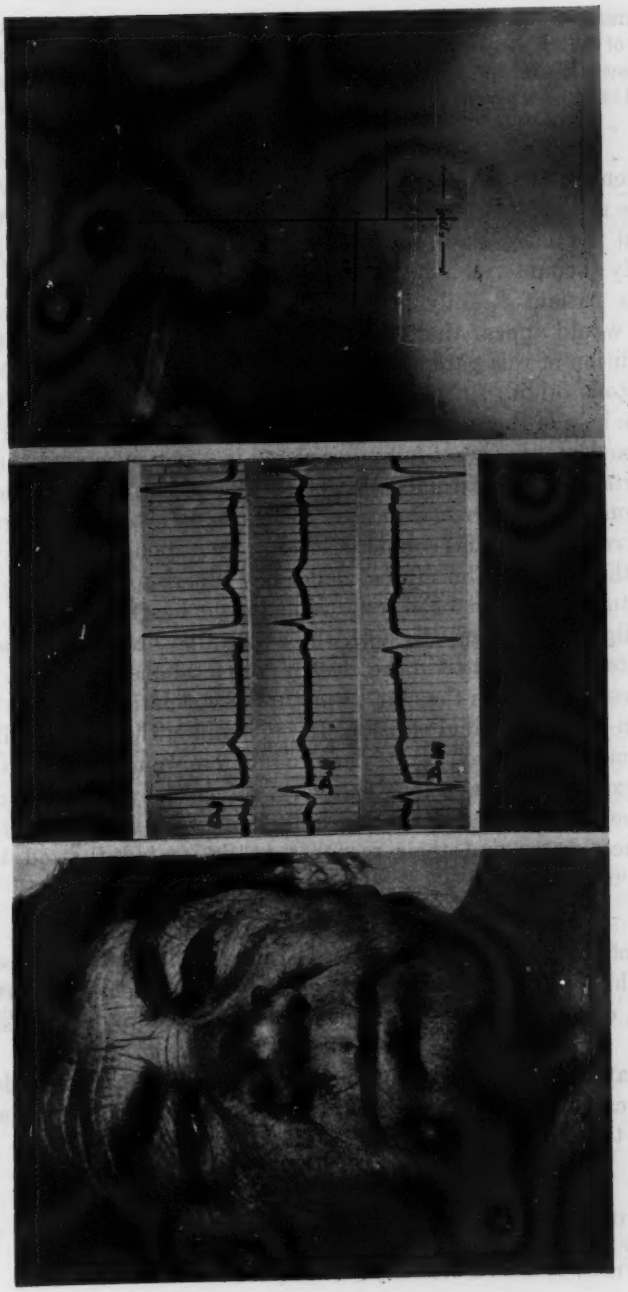

FIG. 2. After nine months of treatment with desiccated thyroid.

sec. Arm to lung = 8 sec. Fluoroscopy showed a moderately enlarged heart due to an enlargement of the left ventricle. *E.C.G.*(Increased voltage of *P*, *QRS*, and *T* waves persisted. Abdomen: No ascites. Liver and spleen not palpable. B.M.R.: plus 31 per cent. R.B.C. count: 4,210,000 per cu. mm. Hemoglobin: 71 per cent.

DISCUSSION

The patient presented clearly has both myxedema and congestive heart failure. The normal basal metabolic rate on admission to the hospital does not rule out the diagnosis of myxedema, as increased basal metabolic rate is frequently encountered in heart failure.

Since the patient steadily improved under treatment with desiccated thyroid, it would appear that thyroid deficiency was an important factor in the condition of this patient. The cardiac insufficiency was probably of myxedematous origin, since it cleared up with desiccated thyroid alone without the help of the standard therapy for congestive heart failure.

This myxedematous heart failure occurred in a patient already suffering from hypertention and cardiac enlargement. The electrocardiogram taken on admission is suggestive of disease of the coronary arteries. Nevertheless, these relatively mild lesions could not be entirely responsible for the clinical picture of the patient. The thyroid deficiency superimposed on the hypertensive picture must have been responsible for the heart failure.

We attribute the dropsy to both the congestive heart failure and the myxedematous disturbance in the electrolyte metabolism.

An interesting point in the clinical picture of our patient was the finding of a protein-rich pericardial effusion. In our opinion this abnormality was due to the myxedema itself rather than to inflammation. High protein content of myxedematous effusions has been observed by Evans and Beretervide. The common finding of high protein content in the cerebrospinal fluid in these cases and their response to desiccated thyroid therapy strengthen our opinion.

SUMMARY

A case of myxedema and congestive heart failure with dropsy and effusion of high protein content has been presented. The manifestations of myxedema, dropsy, and heart failure improved on therapy with desiccated thyroid.

The literature on this subject has been reviewed, and it is concluded that the dropsy can be due either to a disturbance in the electrolyte metabolism alone or to this factor accompanied by congestive heart failure.

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Association Announcement

Nominations for Awards of the Association

Three awards for meritorious work in endocrinology will be given at the next annual meeting of the Association. These include the Squibb and Ciba Awards which have been given in the past and a new award which will be known as the Ayerst, McKenna & Harrison Fellowship in Endocrinology, to be given for the first time in 1947. A special committee of five members of the Association chooses the recipients of these Awards, subject to ratification by the Council, and each member of the Association has the privilege of making one nomination for each award.

Nominations for the Awards should be made on special application forms which may be obtained from the Secretary. A nomination should be accompanied by a statement of the importance of the nominee's contributions to endocrinology and by a bibliography of his most important papers with reprints if possible. Application forms may be obtained from the secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City 3, Oklahoma. All nominations should be sent to his office not later than March 15, 1947.

THE E. R. SQUIBB AND SONS AWARD

The E. R. Squibb and Sons Award of $1,000.00 was established in 1939. It was given in 1940 to Dr. George W. Corner, in 1941 to Dr. Philip E. Smith, in 1942 to Dr. Fred C. Koch, in 1944 to Dr. Edward A. Doisy, in 1945 to Dr. E. C. Kendall, and in 1946 to Dr. Carl G. Hartman. No award was made in 1943. No age or other special limitation is stipulated by the Donor of the Award. So far it has been given for long-continued work of a high quality.

THE CIBA AWARD

The Ciba Award was established in 1942 and is to be given to an investigator not over 35 years of age. No recipient was selected in 1943. In 1944 the Award was given to Dr. E. B. Astwood, in 1945 to Dr. Jane Anne Russell and in 1946 to Dr. Martin M. Hoffman. The Award is for $1,200.00. If the recipient chooses to use the Award to aid in working in a laboratory other than the one in which he normally is located, the Award will be increased to $1,800.00.

THE AYERST, McKENNA & HARRISON FELLOWSHIP

This award was authorized by the Council at the 1946 meeting in San Francisco and will be presented for the first time at the 1947 annual meeting in Atlantic City. The annual stipend is $2,500.00 and may be renewed at the discretion of the Committee on Awards. Applicants for this fellowship shall fulfill the following requirements:

1. They must possess the degree of Doctor of Philosophy or Doctor of Medicine or their equivalent. It is suggested that no restriction be placed on age, but that preference be given to applicants who have recently completed requirements for their Ph.D. or M.C.D. degree.
2. They must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals.
3. They must submit a program of proposed study.
4. They must indicate one or more institutions where the proposed program shall be carried out.
5. They must submit statements of approval from the investigators with whom they propose to conduct their research.
6. They must serve full time if awarded a fellowship. A small amount of time (10 to 15 per cent) may be allotted for course work or for participation in teaching, the latter purely on a voluntary basis.

Association Notice

The 29th annual meeting of the Association for the Study of Internal Secretions will be held Friday and Saturday, June 6th and 7th, 1947, in the Viking Room of Haddon Hall Hotel, Atlantic City, New Jersey, preceding the Centennial meeting of the American Medical Association.

Members are urged to make reservations immediately inasmuch as the hotels expect to be filled to capacity. Make your reservations directly with Chalfonte-Haddon Hall advising them of the accommodations you wish. Rates are as follows:

	Chalfonte	Haddon Hall
Single room with bath:	$6, $7, $9	$7, $8, $10
Double room with bath (without ocean view):	$8 and $10	$10 and $12
Double room with bath (side ocean view):	$12	$14
Double room with bath (ocean front):	$14 and $16	$16 and $18

Make your reservations now and avoid disappointment—remember, you can always cancel them at a later date.

Those wishing to present papers should send the title of the paper and four copies of a comprehensive abstract to the president, Dr. Fuller Albright, Massachusetts General Hospital, Boston, Massachusetts, at their earliest convenience. Abstracts submitted should be in proper form for printing in the program. Not more than the first two hundred words can be included in the printed abstract.

Further information regarding the meeting will be forthcoming at an early date.

Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor; D. A. McGINTY. *Collaborators:* A. R. ABARBANEL, F. N. ANDREWS, B. L. BAKER, F. A. DE LA BALZE, ISRAEL BRAM, R. A. CLEGHORN, RUCKER CLEVELAND, C. D. DAVIS, ANNA FORBES, M. B. GORDON, H. S. GUTERMAN, M. M. HOFFMAN, R. G. HOSKINS, C. D. KOCHAKIAN, H. S. KUPPERMAN, H. L. MASON, JANET W. MCARTHUR, THOMAS H. MCGAVACK, A. E. MEYER, K. E. PASCHKIS, A. B. PINTO, J. R. REFORZOMEMBRIVES, E. C. REIFENSTEIN, JR., G. G. RUDOLPH, L. T. SAMUELS.

MARKSON, C. A. The concurrent use of liver and thiouracil. *Canad. Med. Assoc. Journ. 55* (1): 23–24 (1946).

Thirteen thyrotoxic patients received, together with the usual doses of thiouracil, two cc. of crude liver or one cc. of concentrated liver parenterally twice weekly. In this series one case of agranulocytic angina occurred. In a second series of 20 cases of thyrotoxicosis treated with thiouracil, the patients received Wilson's solubilized liver (Fraction L) orally in daily doses of 20 capsules, 0.5 gm. each. In this series there were two cases of granulocytopenia. The author concludes that liver given simultaneously with thiouracil is ineffective in protecting against agranulocytosis.—*K.E.P.*

STUART, C. K. Thyrotoxicosis, diabetes and thiouracil. *Canad. Med. Assoc. Journ. 55* (2): 150–151 (1946).

A case report on one case of diabetes mellitus and thyrotoxicosis is given: The initial B.M.R. was plus 67, the fasting blood sugar 333 mg. per cent, and there was plus four glycosuria. The patient had not received iodine medication. Treatment consisted of a diet of 2150 Cal., Protamin Zinc Insulin 20 U., supplemented with varying amounts of regular insulin on the basis of the tests. Thiouracil was given in daily doses of 0.4 gm. for 6 days, then decreased to 0.3 gm. per day. During a period in which the B.M.R. decreased to plus 39, the insulin requirement remained unchanged. Thiouracil medication was not continued up to a full remission, and the patient was subjected to a thyroidectomy. After a transient, immediate postoperative rise, the insulin requirement dropped to one-half of the preoperative dose. From observation of this case, the author draws the conclusions that decrease of B.M.R. is not accompanied by decrease of insulin requirement, that pituitary hyperactivity is responsible for aggravation of diabetes mellitus accompanied by thyrotoxicosis, and that thiouracil is not a substitute for operation in restoring the endocrine balance.—*K.E.P.*